IPSO-NITRATION STUDIES

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CONTENTS

ABSTRACT

Reaction of 2,4,6-trialkyl phenols with nitrogen dioxide in organic solvents is known to yield trinitro and dinitro hydroxy cyclohexenones as major products of reaction. These compounds have been postulated as forming *via* the transient intermediacy of 6-nitrocyclohexa-2,4-dienones. In the first part of the thesis the reactions of the C6-benzyl analogues of 4-*t*-butyl-2,6-dimethylphenol (206) and 2-*t*-butyl-4,6-dimethylphenol (216), compounds (229) and (230) respectively, with nitrogen dioxide are shown to give products analogous to those observed in the reactions of the parent phenols. Reaction of 6-benzyl-4-*t*-butyl-2,6-dimethylcyclohexa-2,4-dienone (229) with nitrogen dioxide in benzene solution is shown to give all four stereoisomeric 2,5-dinitrocyclohex-3-enones (240)-(243), and three of the four possible stereoisomeric 2-hydroxy-5-nitrocyclohex-3-enones (244)-(246). In contrast, reaction of 6-benzyl-2-*t*-butyl-4,6-dimethylcyclohexa-2,4-dienone (230) with nitrogen dioxide in dichloromethane solution is shown to yield cyclohex-2-enones as the major products of reaction - namely, the four stereoisomeric 4,5-dinitrocyclohex-2-enones (231)-(234). The cyclohex-3-enones (235)-(238) are isolated as minor products of reaction.

In the second part of the thesis, the reactions of *p*-cymene (401) with nitrogen dioxide in acetic anhydride and dichloromethane solutions are explored. In dichloromethane solution, all the products of reaction, with the exception of 2-nitro-*p*-cymene (403) and *p*-nitrotoluene (405), can be accounted for in terms of a mechanism involving initial hydrogen atom abstraction from the *iso*-propyl group of the *p*-cymene molecule. In contrast, the reaction of *p*-cymene in acetic anhydride solution is shown to yield a multitude of products, including 2-nitro-*p*-cymene (403) and *p*-nitrotoluene (405), the two substituted aromatic compounds (414) and (415), and the eleven substituted cyclohexenes (410)-(413), (416)-(421) and (434). The mode of formation of these cyclohexenes in particular, is discussed in terms of an overall mechanistic scheme for the reaction of *p*-cymene in acetic anhydride solution.

Throughout the thesis, extensive use is made of single crystal X-ray structure analysis, and high field Fourier transform n.m.r. techniques, in determining molecular structure. The structures of fifteen compounds have been determined by single crystal X-ray structure analyses.

CHAPTER ONE

INTRODUCTION

Aromatic nitration has long been recognized as one of the most important reactions in organic chemistry. Since Faraday's first recorded nitration of benzene with nitric acid in 1825[1], nitration reactions have been extensively studied. The importance of nitration chemistry is twofold: first, it offers the simplest route to the production of aromatic nitro compounds; and second, it has been the basis for the development of the theory of electrophilic aromatic substitution.

The extensive use in industry of nitro compounds, both as important precursors to other substituted aromatic compounds (*e.g.* amines, and subsequent production of azo-dyes), and as useful compounds in their own right (*e.g.* explosives), attest to the huge importance of nitration reactions in organic chemistry. However, despite this widespread industrial usage, and the many studies made regarding the mechanisms of such nitration reactions, speculation regarding the mechanism of nitration continues, and as Schofield stated in his book on aromatic nitration in 1980[2]: "there are still surprises to come."

1.1 ELECTROPHILIC AROMATIC SUBSTITUTION

Electrophilic (ionic) aromatic substitution (EAS) reactions have been the subject of many theoretical and experimental studies. The commonly accepted mechanism for these reactions is summarized in Figure 1.1, below.

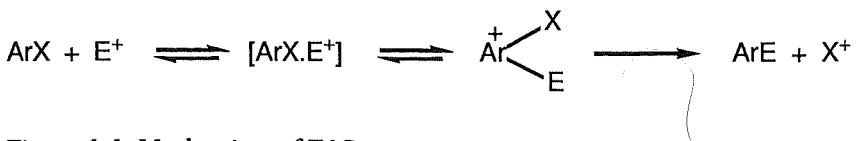


Figure 1.1 Mechanism of EAS.

The electrophile and the aromatic diffuse together to give an encounter pair [ArX.E^+], which subsequently gives rise to the unstable Wheland inter-

mediate (or σ-complex). The exact form of the encounter pair, and its conversion to the Wheland intermediate remains uncertain. The final substituted product ArE, forms from the Wheland intermediate by a loss of X^+.

1.1.1 Conventional electrophilic attack

In conventional electrophilic (ionic) aromatic substitution reactions of mono-substituted benzenes, the attacking electrophile binds at a non-substituted position on the aromatic ring, and so "X" in the above equation (Figure 1.1) is a hydrogen atom. There are three possible Wheland intermediates, formed from initial electrophilic attack *ortho*, *meta*, and *para* to the substituted position, and known as W_o, W_m and W_p respectively. Figure 1.2 illustrates the Wheland intermediates for the nitration of nitrobenzene (101).

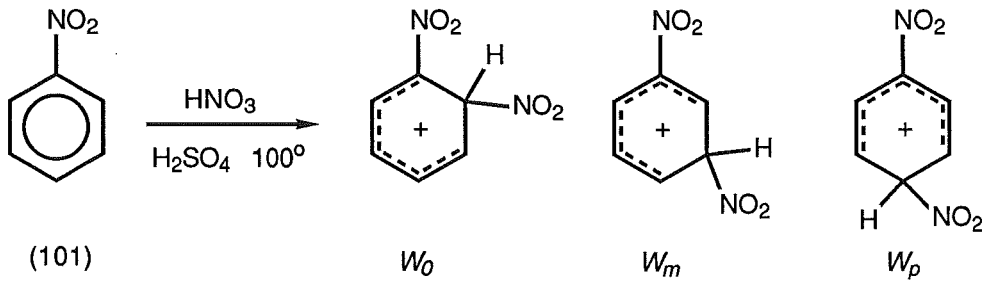


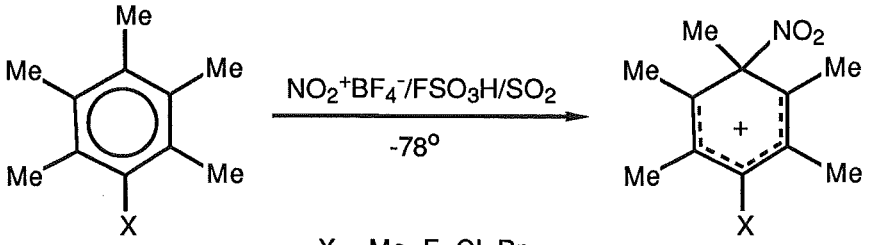
Figure 1.2 Wheland intermediates in the nitration of nitrobenzene (101).

Although direct observation of W_o, W_m and W_p is very difficult, indirect evidence for the existence of such intermediates is very strong, as they allow a ready explanation of the directing effects and product ratios observed in such electrophilic (ionic) substitution reactions. The chemistry of these intermediates is generally limited to proton loss, to form the substituted aromatic product.

1.1.2 Electrophilic *ipso* attack

A fourth type of Wheland intermediate is formed when the initial electrophilic attack occurs at a substituted position on the aromatic ring. The prefix *ipso* was coined by Perrin and Skinner[3] to denote this type of

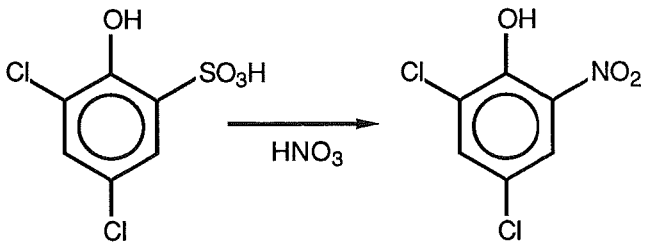
attack. In contrast to the three Wheland intermediates discussed above, the Wheland intermediates from *ipso* attack can be isolated under certain conditions. For example, some hexasubstituted benzenes (102) give relatively stable Wheland intermediates (103) (Figure 1.3), the structures of which have been established by n.m.r. spectroscopy.[4]



(102) (103)

Figure 1.3 *Ipso* Wheland intermediate in the nitration of hexasubstituted benzenes.

Products arising from initial *ipso* attack have long been known. As early as 1871 Armstrong reported the nitrodesulphonation reaction of 2-hydroxy-3,5-dichlorobenzene sulphonic acid (104),[5] a reaction which can only be rationalized by assuming an initial *ipso* attack by nitronium ion.



(104)

Figure 1.4 Nitration of 2-hydroxy-3,5-dichlorobenzene sulphonic acid.

Despite the existence of such examples in the literature, generally these reaction products were regarded as being products of anomalous or non-conventional nitration.[6] It is only recently that these effects have been discussed as a separate, identifiable area of nitration chemistry,[7] and that these seemingly anomalous reaction products have been rationalized as being consequences of *ipso* attack.

1.1.3 Radical *ipso* attack

The electrophilic radical $\dot{N}O_2$, will combine with aromatic systems to give radical Wheland intermediates, in an analogous manner to that described above for electrophilic ionic reactions (Section 1.1.2). For example, reaction of anthracene (105) with nitrogen dioxide involves an initial radical attack at C9, to form a resonance stabilized, radical Wheland intermediate (106), as illustrated in Figure 1.5.

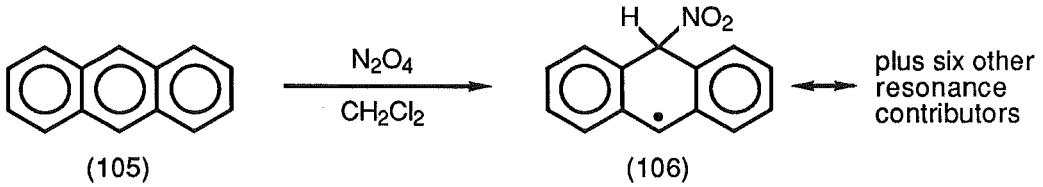


Figure 1.5 Radical Wheland intermediate in the nitration of anthracene.

The reactivity of such intermediates toward other unpaired electron species is very high, and they undergo subsequent radical coupling reactions to generate the observed products. Analysis of the likely location of the unpaired electron (upé) spin density in such radical Wheland intermediates, will indicate the most probable sites at which this radical coupling reaction will occur. Thus, in the example above, the nitroanthracenyl radical (106) couples almost exclusively at C10, yielding dinitro products,[8] or 9-nitroanthracene[9] (formed by loss of HNO_2 from the dinitro compound) as the major products of reaction. A more detailed discussion of the chemistry and reactions of nitrogen dioxide is presented in the following section.

1.2 DINITROGEN TETROXIDE AND NITROGEN DIOXIDE

Although the majority of the literature is concerned with nitration *via* electrophilic aromatic substitution, where the active nitrating species is the nitronium ion (NO_2^+), there are also significant references[10,11,12] to free-radical nitration by the lower oxides of nitrogen, N(III) and N(IV). Indeed, the last ten years has seen renewed interest in this field, particularly in the reactions of polycyclic aromatic hydrocarbons (PAHs) with nitrogen dioxide, as the potential environmental effects of this type of nitration in the atmosphere are explored.

1.2.1 Physical characteristics and properties of N_2O_4

Dinitrogen tetroxide freezes at -11.2°,[13] and below this temperature exists as a white solid, the structure of which (ignoring bond multiplicities) is illustrated in Figure 1.6.

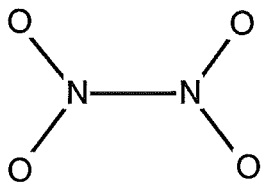


Figure 1.6 Structure of N_2O_4.

X-ray analysis of the solid reveals a bond length of 1.17Å for all N-O distances, a bond length of 1.64Å for the N-N distance, and an O-N-O angle of 126°. At liquid helium temperatures, other structures have been reported for N_2O_4[14] but these are not considered to be significant at normal temperatures.[15]

At room temperature dinitrogen tetroxide exists as an equilibrium mixture of dinitrogen tetroxide and nitrogen dioxide radicals ($\dot{N}O_2$), the equilibrium being established by homolytic dissociation of the N-N bond of N_2O_4. The relative composition of the equilibrium mixture is strongly temperature dependent. In the liquid state, between -11.2° and 21.2°, the system may be considered a dilute solution of $\dot{N}O_2$ in N_2O_4, the dimer being the predominant species, whereas the vapour at 100° consists mainly (*c.* 90%) of monomeric nitrogen dioxide rdicals.

1.2.2 The nitrogen dioxide radical, $\dot{N}O_2$

The monomeric, unpaired electron species $\dot{N}O_2$ has been subjected to extensive e.s.r. spectroscopic investigations, in order to determine the location of the unpaired electron (upé) spin density. Solution studies of $\dot{N}O_2$ in non-polar, non-coordinating solvents reveal little,[16] presumably because dimerization to N_2O_4 is very rapid. The vast majority of e.s.r. studies on $\dot{N}O_2$ have been conducted on systems where the radical is "trapped" in an inert matrix.[17,18,19] These studies reveal that the upé spin density is distributed so that approximately 50% is located on the nitrogen atom, with the remaining 50% being shared between the two oxygen atoms. These studies also report a calculated O-N-O angle of 132-134°, very similar to the gas phase value of 134°.[20]

In addition to its upé character, $\dot{N}O_2$ has an electric dipole moment (0.316 D*), a consequence of the differing electronegativities of nitrogen and oxygen. This gives the nitrogen centre of the radical significant electrophilic character, while the oxygen centres are somewhat nucleophilic in nature. Indeed, the nature of the $\dot{N}O_2$ radical can be well approximated by the four resonance contributors illustrated in Figure 1.7, which take into account both the upé spin density distribution, as well as the effect of the electric dipole moment.

Figure 1.7 Canonical forms for the nitrogen dioxide radical.

1.2.3 The effect of solvents on the N_2O_4/NO_2 equilibrium

Dissolution of N_2O_4 in organic solvents has a marked effect on the nature of the N_2O_4/NO_2 equilibrium. In the gas phase the equilibrium constant (K_c^{298}) is $1.51*10^{-1}$ mol l^{-1},[21] but this value is reduced to $1.77*10^{-4}$ mol l^{-1} in non-coordinating solvents such as cyclohexane and carbon tetrachloride.[22] This decrease is attributed to a drastic lowering of the entropy of dissociation with respect to the gas phase, as little change is observed in the enthalpy of dissociation. A further reduction in K_c^{298} is observed in coordinating solvents like acetonitrile or acetic anhydride (K_c^{298} (CH_3CN) $0.3*10^{-4}$ mol l^{-1}). The additional decrease in K_c^{298} is attributed in this case to an association of the N_2O_4 molecule with the solvent, this association being reflected in an increase in the enthalpy of dissociation of N_2O_4.

1.2.4 Adducts of N_2O_4 with organic solvents

The existence of solid, molecular addition compounds between dinitrogen tetroxide and certain organic solvents is recognized by thermal analysis of the binary systems.[23,24] These analyses reveal that the solid form of the

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* One Debye (D) = 10^{-18} e.s.u. cm.

addition compound, formed by partial freezing of the liquid mixture, melts at a temperature quite different from that indicated by the established phase diagram.

Evidence for a similar coordination of N_2O_4 with certain solvent molecules in solution, is reported by Addison *et al.*[25,26,27] They noted that for those solvents which contain an atom which has one or more lone pairs of electrons available (onium donor solvents), addition compounds are formed with N_2O_4, the dinitrogen tetroxide molecule acting as an electron acceptor. Their summary of the interactions involved are presented in Figure 1.8.

$$(Don)_n.N_2O_4 \rightleftharpoons n(Don) + N_2O_4 \rightleftharpoons [(Don)_nNO]^+NO_3^-$$

Figure 1.8 Interactions of N_2O_4 with donor solvents.

These molecular interactions are reflected by changes in the physical properties of the solvent. Significant deviations in freezing point,[25] vapour pressure,[26] viscosity,[27] and reactivity[25] are observed, which are not encountered in similar solutions of N_2O_4 in non-coordinating solvents. However, as most organic onium donor solvents are only weak electron donors, the adducts are not present in sufficient quantity to be readily detected by infrared or ultraviolet spectroscopy.[15,28] The exact nature of the adducts in solution remains uncertain. Addison *et al.* originally proposed an ionic structure, $[(Don)_n.NO^+]NO_3^-$, to account for the vastly increased reactivity of N_2O_4 towards metals in the presence of donor solvents, but the failure to observe any significant effects in the ultraviolet spectrum, and the relatively low conductivity of such solutions, led them to suggest that "although partial electron-transfer undoubtedly occurs, there is no direct evidence for the existence of individual molecules of addition compounds in the liquid state."[27]

1.3 REACTIONS OF NITROGEN DIOXIDE

Solutions of dinitrogen tetroxide in strong acids can be used as nitrating agents, and the active nitrating species is undoubtedly the nitronium ion.[29] Nitrations using this medium follow the general mechanistic pathways discussed in Section 1.1.

Nitration with N_2O_4/NO_2 in organic solvents is also possible, and in contrast to the situation in strong acids, these nitration mechanisms generally involve $\dot{N}O_2$ as the active nitrating species. The free radical reactions of nitrogen dioxide with alkanes and alkyl substituents, alkenes, phenols, and non-phenolic aromatic compounds are discussed below.

1.3.1 Reactions of nitrogen dioxide with alkanes

Nitrogen dioxide reacts with alkane systems, and alkyl side chains of aralkyl systems, *via* hydrogen atom abstraction to give alkyl radicals. Thus, nitration of toluene (107) occurs by abstraction of one of the hydrogen atoms of the methyl group, to give a carbon centred benzyl radical (108), followed by a radical coupling reaction of this radical with a further molecule of nitrogen dioxide to yield 1-nitro-1-phenylmethane (109).[10,30] The reaction scheme is summarized in Figure 1.9.

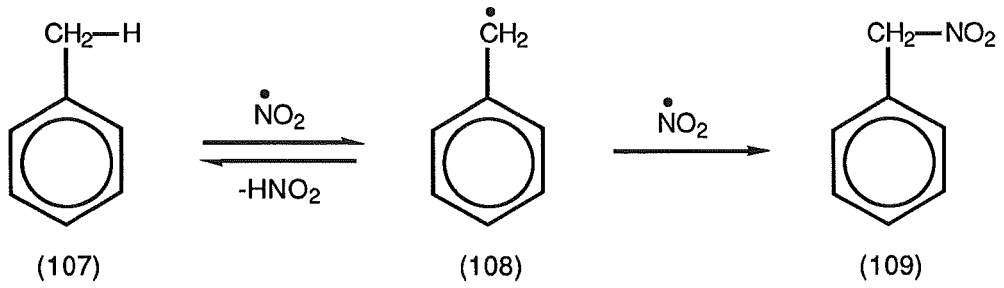


Figure 1.9 Nitration of toluene by nitrogen dioxide.

1.3.2 Reactions of nitrogen dioxide with alkenes

Nitrogen dioxide can react with olefinic systems by two separate pathways, one involving addition to the double bond, and the other involving allylic substitution. Both of these reaction pathways are postulated as proceeding *via* free radical mechanisms.[31] The radical addition process is the more commonly observed process, and indeed the rate of reaction *via* this mechanism far exceeds the rate for the allylic substitution process, except at very low nitrogen dioxide concentrations.

1.3.2.1 The currently accepted mechanism for the radical addition of nitrogen dioxide to alkenes is summarized in Figure 1.10.

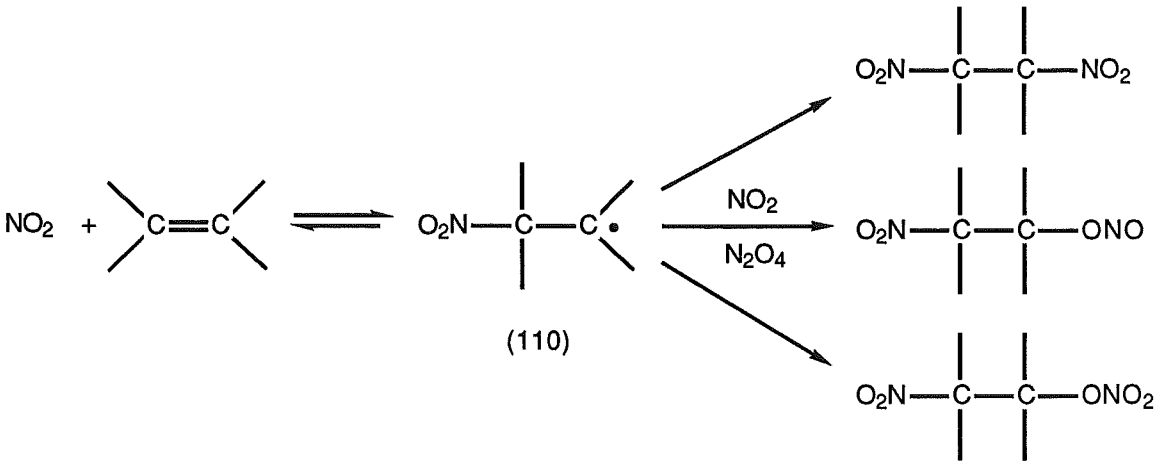


Figure 1.10 Addition mechanism for the nitration of alkenes with nitrogen dioxide.

The products observed are vicinal dinitro alkanes, nitro nitrites, nitro alcohols, and nitro nitrates, the relative concentrations of which are dependent on the substrate, as well as the reaction and workup conditions. The initial reaction involves a reversible[10,32] addition of nitrogen dioxide to the double bond to form the carbon centred radical (110) (see Figure 1.10, above). Radical (110) then reacts with a further molecule of nitrogen dioxide (with bond formation to either the nitrogen or the oxygen centre) to give the observed products. The detection of radical intermediates by e.s.r. spectroscopy during the reaction of styrene with nitrogen dioxide[33] provides strong evidence for the free radical mechanism. Furthermore, Brand and Stevens[34] demonstrated that when the nitration of cyclohexene with nitrogen dioxide was carried out in the presence of a radical transfer agent ($BrCCl_3$), none of the normally observed dinitro or nitro nitrito compounds were isolated, but that the major product of reaction was 1-bromo-2-nitrocyclohexane, produced by reaction of the 2-nitrocyclohexyl radicals (formed by initial nitrogen dioxide addition to the alkene) with bromotrichloromethane. They concluded that "the total suppression of the 'normal' products must mean that the heterolytic reaction, if it operates at all, is of very minor importance." Further evidence for the radical mechanism comes from the nitration of norbornene (111) with nitrogen dioxide.[31,35] The only two dinitro compounds isolated were those illustrated in Figure 1.11 below, with no evidence for compounds arising from nitrogen dioxide addition to a rearranged norbornyl cation intermediate, which would be expected if the reaction was proceeding by a heterolytic mechanism.

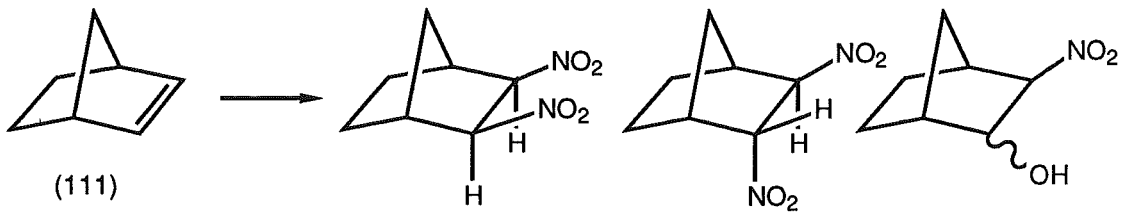


Figure 1.11 Nitration of norbornene (111) with nitrogen dioxide.

Moreover, the rate of the norbornene reaction is comparable with the rates of other alkene nitration reactions, which would not be the case if the norbornene reaction pathway involved a highly stabilized, norbornyl cationic intermediate.

One facet of the alkene nitration mechanism which remains uncertain is the origin of the nitrate compounds observed. The amount of nitro nitrate observed in the reaction product mixture is highly dependent on the reaction conditions. It is known that oxygenation of the system results in an increased formation of nitrate products,[35,36,37] although Bonetti *et al.*[38] found that in certain solvents (onium donor solvents) nitrate formation was increased, in the absence of oxygen, by lowering the temperature of the reaction. Three possible mechanisms have been proposed to account for the observed formation of nitro nitrates,[36,38,35,31] and these are presented in Figure 1.12 below.

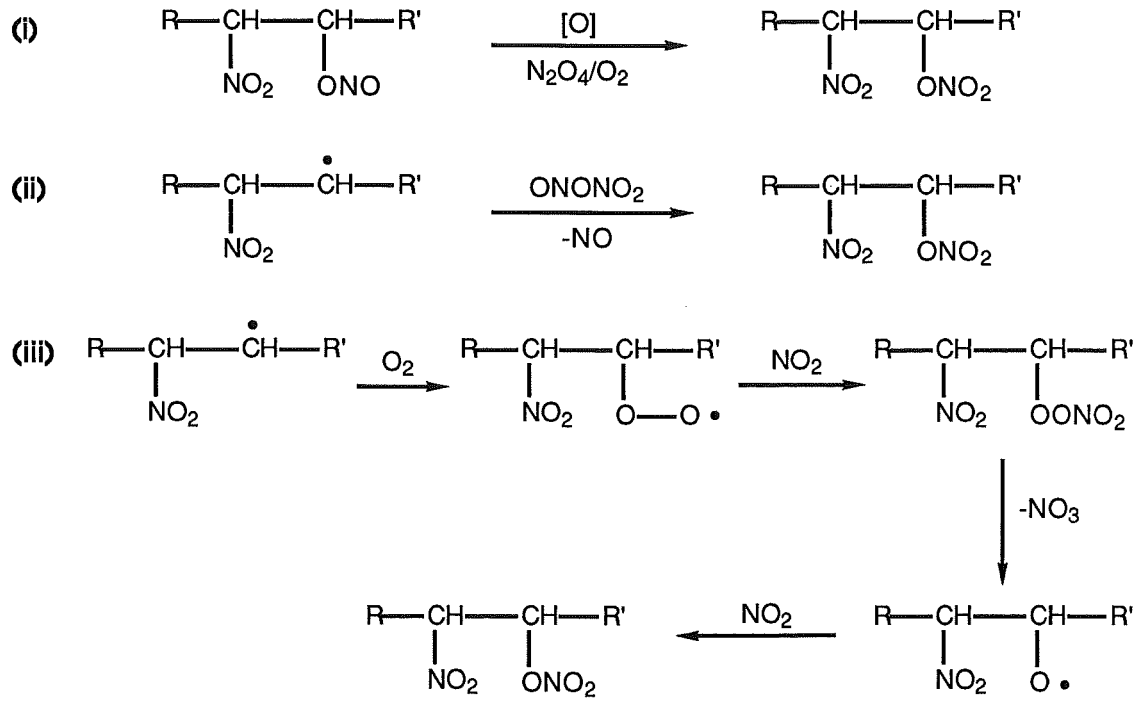


Figure 1.12 Postulated mechanisms for nitro nitrate formation during alkene nitration.

1.3.2.2 The alternative pathway for the reaction of olefinic systems with nitrogen dioxide, occurs *via* an initial allylic hydrogen atom abstraction, and results in an overall allylic substitution. The mechanism for the hydrogen abstraction initiated allylic substitution is summarized in Figure 1.13.

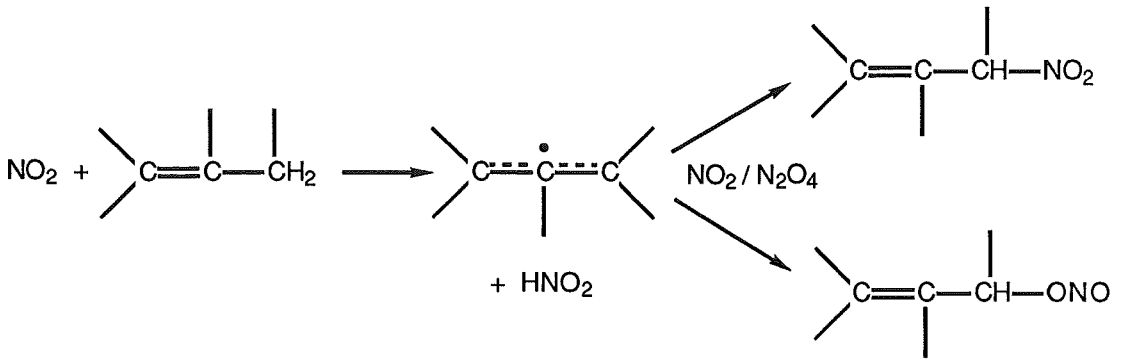


Figure 1.13 Substitution mechanism for the nitration of alkenes with nitrogen dioxide.

This substitution process is only observed at very low nitrogen dioxide concentrations,[31,39] a fact which can be rationalized by direct comparison of the mechanisms for the two competing processes (addition and substitution). Addition, although being the thermodynamically favoured process, is reversible[32] (see Figure 1.10), whereas the hydrogen abstraction process is not. Hence, at high concentrations of nitrogen dioxide, a large proportion of the carbon centred radicals (110) (Figure 1.10), react to give products. At very low concentrations of nitrogen dioxide, the radical (110) is trapped more slowly and a larger fraction reverts to the starting alkene. Consequently less addition products are observed, and the abstraction process becomes favoured. The Table below (Figure 1.14) illustrates this change in the predominant mechanism, from addition to substitution, for the reaction of cyclohexene with nitrogen dioxide.[39]

(wt% NO_2)	37.0	0.20	0.008
Substitution products			
2-cyclohexenol	1	15	69
3-nitrocyclohexene	5	27	13
Addition products			
1-nitrocyclohexene	33	13	2
2-nitrocyclohexanol	61	39	3

Figure 1.14 Mole percentage of products formed in the nitration of cyclohexene. 1-nitrocyclohexene is formed by HNO_2 elimination from dinitrocyclohexane.

1.3.3 Reactions of nitrogen dioxide with phenols

Nitrogen dioxide reacts with phenols by abstraction of the labile phenolic hydrogen atom, generating phenoxy radicals. The presence of these highly delocalized radicals, as intermediates in the reaction pathway, has been demonstrated by electron spin resonance (e.s.r.) spectroscopic studies on the nitration reaction of 2,6-di-*t*-butyl-4-methylphenol.[40] E.s.r. spectroscopic measurements of phenoxy radicals have also been used to determine the proportion of the unpaired electron (upé) spin density at the various ring positions.[41,42,43] These calculations reveal that maximum upé spin density occurs at C4, with lesser amounts at C2, C6, C1 and the oxygen atom, and a "negative" spin density at C3 and C5. These results are in accord with the observed frequency of attack on the phenoxy radical by other upé species: C4 > C2, C6 > C1, O >> C3 and C5. Although the extensive delocalization of the upé spin density means phenoxy radicals are reasonably stable under certain conditions (this is especially the case for those phenoxy radicals with a 2,4,6-trisubstitution pattern[44]), they are extremely reactive towards other upé species such as nitrogen dioxide.

Radical coupling between phenoxy radicals and nitrogen dioxide occurs to give 4-nitrocyclohexadien-2,5-ones (112) (Figure 1.15), in agreement with the upé spin density measurements above. These 4-nitrodienones (112) are reasonably inert to further reaction with nitrogen dioxide and can be isolated under certain conditions.[40,45,46,47]

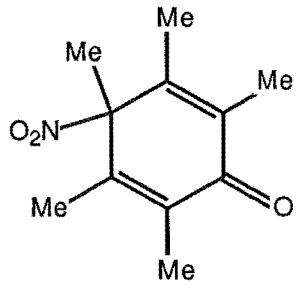


Figure 1.15
4-nitrodienone (112) from pentamethylphenol.

As a consequence of their relative inertness towards further radical attack, the commonly observed mode of reaction of these 4-nitrodienones involves a rearrangement to the corresponding 6-nitrocyclohexa-2,4-dienone. This rearrangement is envisaged as occurring *via* homolysis of the C4-nitro bond, followed by a 1,3-nitro group migration, the whole process occurring within a solvent cage.[48] In contrast to the 4-nitrodienones, the linear conjugation of the diene system present in the 6-nitrodienones means they are susceptible to further radical addition of nitrogen dioxide.[49] The 6-nitrodienone may either react directly with $\dot{N}O_2$, to give in general 2,5-addition products (although 4,5-addition products are also occasionally observed[46,47,50]), or it may rearrange to give the 6-hydroxydienone, *via* a

nitro-nitrito rearrangement of the C6-nitro group. The 6-hydroxydienone then undergoes subsequent 2,5- or 4,5-radical addition, analogous to the addition reactions observed for the 6-nitrodienone. The overall reaction scheme is illustrated below (Figure 1.16) for the reaction of 4-*t*-butyl-2,6-dimethylphenol[51] with nitrogen dioxide in benzene solution.

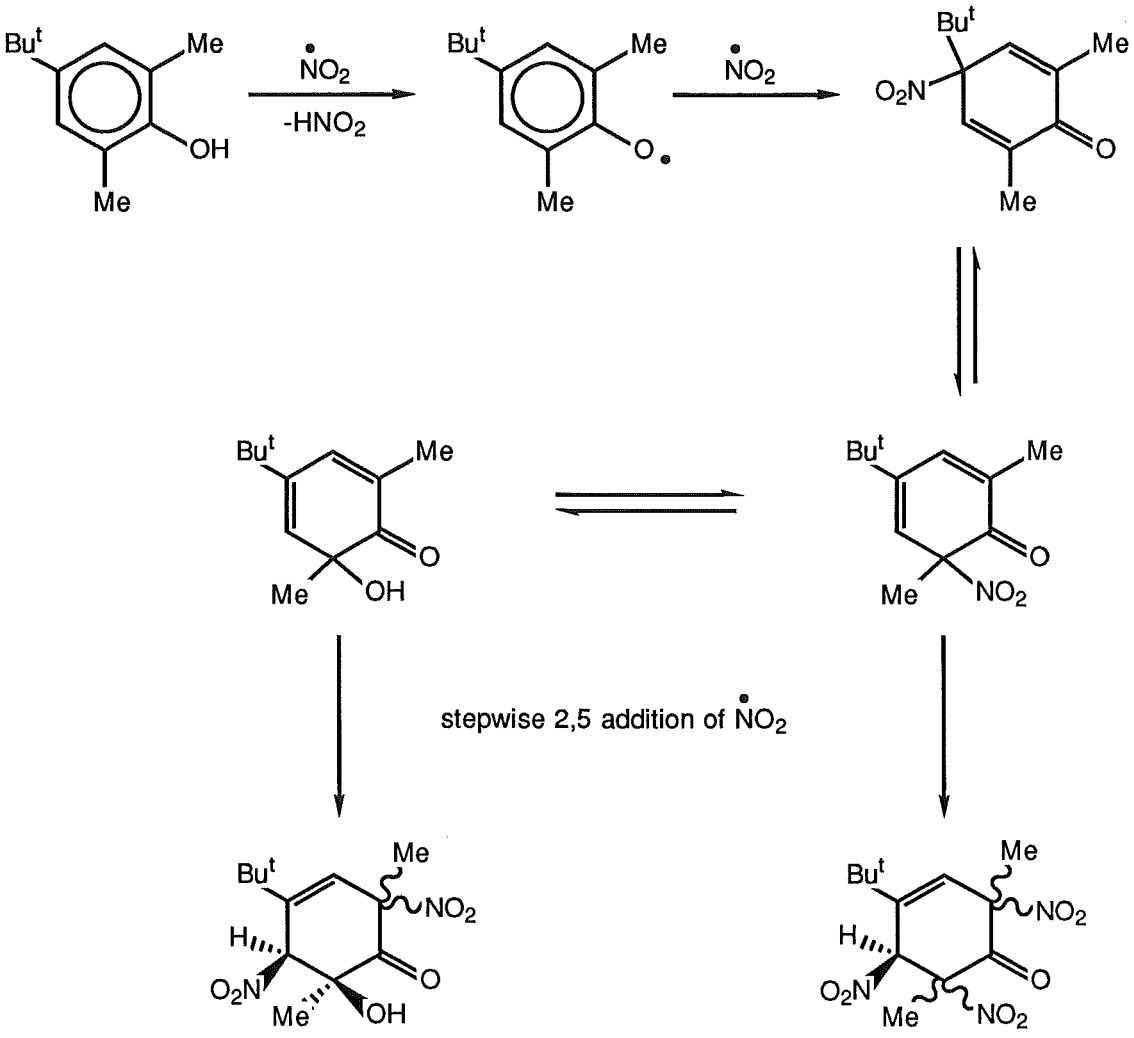


Figure 1.16 Mechanism for the reaction of 4-*t*-butyl-2,6-dimethylphenol with NO_2.

1.3.4 Reactions of nitrogen dioxide with aromatic compounds

The nitration reactions of aromatic compounds under non-acidic conditions have received little comment in the literature prior to the late 1970s, the majority of aromatic nitration work concentrating on reactions carried out in strongly acidic, polar media, where the active nitrating species is generally regarded as the nitronium ion.[2] Recently however, there has been

a renewed interest shown in the reactions of aromatic compounds, in particular polycyclic aromatic hydrocarbons (PAHs), with nitrogen dioxide under non-acidic conditions. The interest stems from the existence of nitrogen oxides in smog (it can be detected in relatively high concentrations in the exhausts from combustion engines), and the known, strong carcinogenic and mutagenic nature of some of the products of reaction between nitrogen dioxide and aromatic hydrocarbons.[52] Despite the recent interest, the mechanism of the reactions between nitrogen dioxide and aromatic systems remains controversial.[53] Indeed, it seems likely that various, different mechanisms operate, the type of mechanism being strongly dependent on both the reaction conditions employed, and on the nature, and reactivity of the substrate itself. Brief comment is made below on the four suggested mechanisms: (i) nitration *via* nitrosation, (ii) nitration *via* free-radical attack by nitrogen dioxide, (iii) nitration involving an initial electron transfer, and (iv) nitration involving electrophilic substitution.

1.3.4.1 Nitration *via* nitrosation In those cases where the aromatic substrate is strongly activated towards electrophilic attack (*e.g.* phenols, anilines, anisoles), it has been shown[54] that the mechanism of nitration involves a nitrous acid catalyzed nitrosation step. Bonner *et al.*[55] have proposed that nitration of *p*-dimethoxybenzene (113) with nitrogen dioxide in carbon tetrachloride solution proceeds *via* a similar mechanism, involving initial nitrosation, and a subsequent oxidation of the nitroso group of compound (114) to a nitro group by N_2O_4 (Figure 1.17).

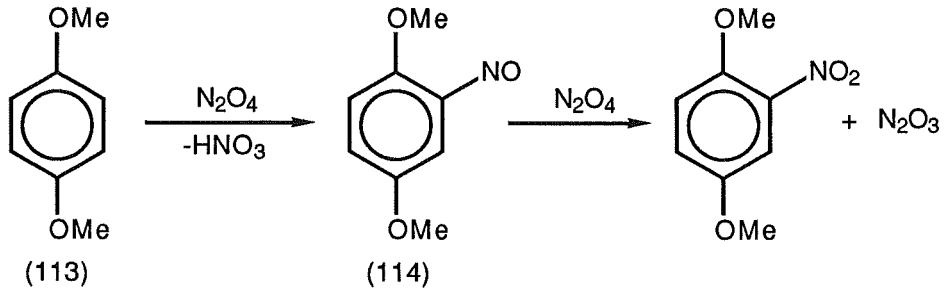


Figure 1.17 The mechanism for reaction of *p*-dimethoxybenzene with nitrogen dioxide.

The effects observed upon addition of certain compounds to the reaction medium, provide evidence for the ionic nature of the mechanism. In particular, a large increase in rate was observed on addition of species likely to stabilize the $NO^+NO_3^-$ ion pair, produced by the heterolytic dissociation of N_2O_4. In addition to the nitrosation mechanism outlined above, additional

mechanisms, involving nitration *via* NO^+ adducts have also been postulated, and these are discussed below (see nitration *via* electrophilic substitution, Section 1.3.4.4).

1.3.4.2 Free-radical nitration Reactions following a free-radical mechanism, where the active nitrating species is the nitrogen dioxide radical have also been reported.[10,53,56] As expected, the radical process becomes more favourable, relative to any ionic processes, as the polarity of the reaction medium is lowered. For example, Pryor *et al.*[53] have reported that in the reaction of fluoranthene (115) with nitrogen dioxide, the homolytic free-radical mechanism becomes favoured when the reaction solvent is changed from dichloromethane to carbon tetrachloride. Figure 1.18 depicts the radical reaction scheme proposed by Pryor *et al.* to account for the observed products.

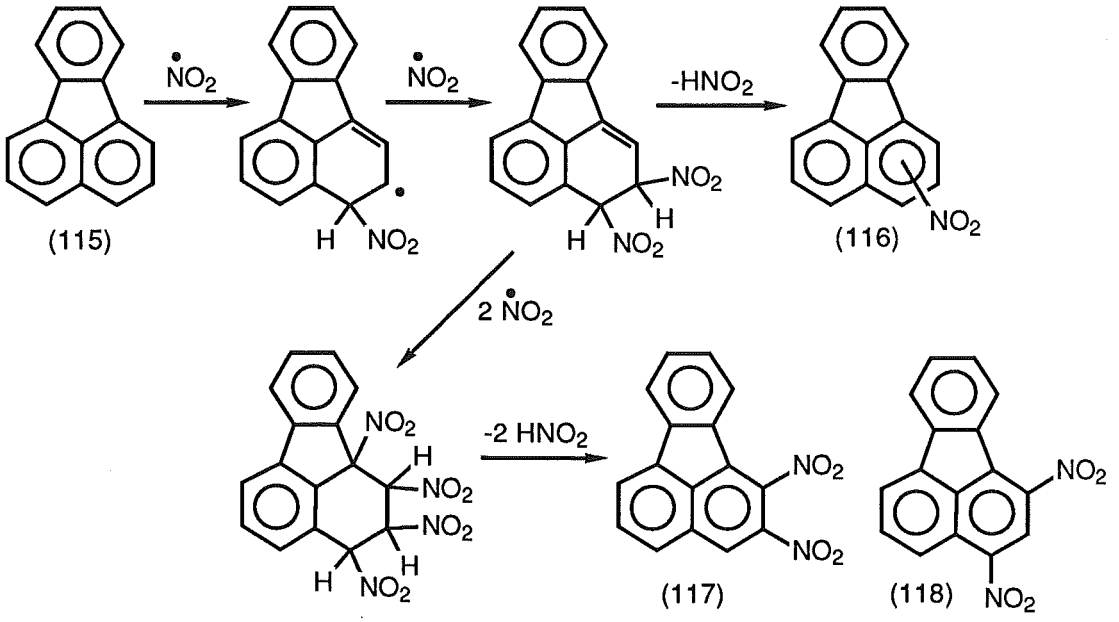


Figure 1.18 The mechanism for reaction of fluoranthene with nitrogen dioxide.

The existence of 2-nitrofluoranthene (116) in the product mixture, in addition to the 3-nitro isomer, lends strong support to the radical mechanism, as the 2-position is the least activated site toward electrophilic attack. Indeed, under standard electrophilic nitration conditions (nitric acid in acetic acid) no 2-nitrofluoranthene is observed.[57] Furthermore, the appearance of small amounts of 1,2-dinitrofluoranthene (117), and 1,3-dinitrofluoranthene (118) as products in the reactions of Pryor *et al.*, lends further support to the radical mechanism, as these products can not easily be accounted for by an electrophilic mechanism.

1.3.4.3 Nitration *via* electron transfer Based on the electron-transfer mechanism for nitration by the nitronium ion proposed by Perrin,[58] Pryor *et al.* postulated a similar electron-transfer mechanism for nitrogen dioxide mediated nitration reactions,[59] utilizing nitrogen dioxide, instead of the nitronium ion, as the electron acceptor. This mechanism is illustrated in Figure 1.19, using naphthalene (105) as an example.

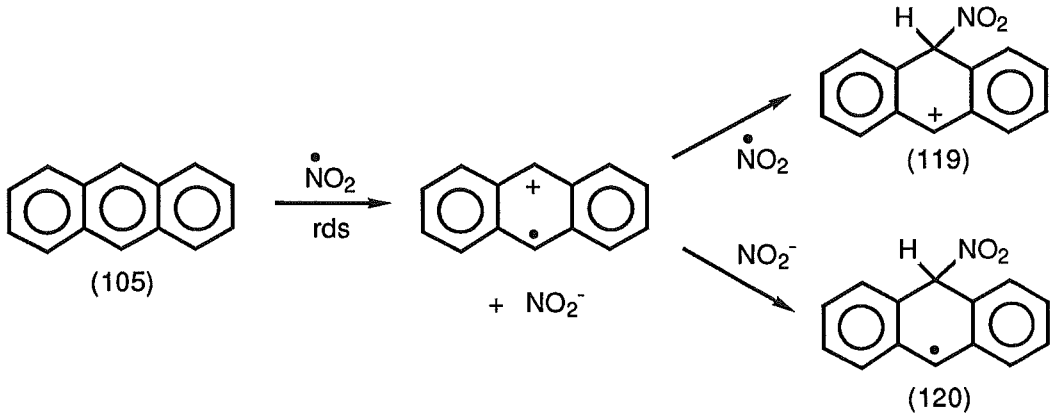


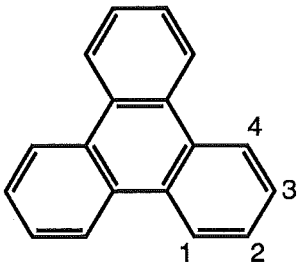
Figure 1.19 Formation of σ-complexes *via* a rate determining electron transfer step.

Following electron transfer, subsequent reaction occurs *via* the two σ-complexes: the cationic σ-complex (119) can react by loss of a proton to give 9-nitronaphthalene, whereas the radical σ-complex (120) probably reacts *via* further addition of nitrogen dioxide, and subsequent elimination of nitrous acid, to yield 9-nitronaphthalene. Determinations of linear free energy relationships between rate data and molecular orbital parameters for a series of PAHs, gave better correlations for an electron transfer rate-determining step, than for a σ-complex rate-determining step. Furthermore, the isolation of significant quantities of 9,10-anthraquinone from the reaction of anthracene with nitrogen dioxide in dichloromethane, is most readily explained by a competing reaction of the intermediate radical cation with water.

1.3.4.4 Nitration with electrophilic substitution A study of the reactions of certain PAHs with nitrogen dioxide in dichloromethane solution, led Eberson and Radner[60] to postulate a fourth mechanism, where initial attack actually occurs *via* a nitrosated dinitrogen tetroxide molecule $N_3O_5^+$. Their reasons for proposing this novel nitrating species were based on a combination of mathematical calculations, and experimental observations. Theoretical calculations on the suitability of NO_2 or NO^+ as electron transfer oxidants, suggested that rate-determining electron

transfer to these, more "typical" species was very unlikely. Furthermore, the observation of very high degrees of positional selectivity, while not in keeping with radical or nitrosation processes, could be accounted for by the increased bulkiness of the $N_3O_5^+$ electrophile, relative to the more conventional NO_2^+.

For example, they observed a high degree (78%) of substitution at the unhindered 2-position in the nitration reaction of triphenylene (121), despite the fact that this is not the most activated position toward electrophilic attack.



Triphenylene (121)

1.4 RECENT ADVANCES IN N.M.R. SPECTROSCOPY

The unambiguous assignment of the structure and stereochemistry of the compounds isolated during the course of this research, is absolutely necessary for informed comment to be made regarding possible mechanisms and modes of formation of those compounds. These structural and stereochemical assignments, which until very recently could only be made with confidence by single crystal X-ray structure analyses, are in this work often made on the basis of n.m.r. spectroscopic data, utilizing many of the pulsed Fourier transform (FT) n.m.r. techniques. This section of the introduction consists of a brief overview of some of these recent advances in n.m.r. spectroscopy.

The introduction of pulse FT n.m.r. methods, coupled with the advent of very high field superconducting magnets, undoubtedly opened a new era in n.m.r spectroscopy. Not only did it offer greatly enhanced sensitivity over the older continuous wave techniques, but it also allowed the development of the various two-dimensional (2-D) n.m.r. techniques discussed below.

The **COSY** (*Correlated Spectroscopy*)[61] experiment is a two-dimensional homonuclear spin correlation experiment, which presents all proton-proton spin couplings on a single 2-D contour plot (See Figure 1.20 below for an example of a contour plot). On a simple time basis this offers a distinct

advantage over the large number of traditional homonuclear decoupling experiments which would be required to obtain the same information. Furthermore, a COSY experiment offers the following additional advantages: (i) to some extent the problem of signal overlap is eliminated, by dispersing the spectrum into two dimensions; (ii) long range couplings, which are difficult or even impossible to determine from one-dimensional experiments, can often be detected readily with the 2-D method; and (iii) the difficulties encountered in the classical homonuclear decoupling experiment, when the frequency difference between the decoupler field and other hydrogen resonances is small, is absent in the COSY experiment, so couplings between hydrogens with very similar chemical shift values can be routinely detected.

The **HETCOR** (*Het*eronuclear *cor*related spectroscopy)[62] experiment is a 2-D heteronuclear spin correlation experiment, which expands the ^{1}H spectrum into the ^{13}C range, so that individual protons can be identified as being bonded to specific carbon atoms in the ^{13}C spectrum. Like the COSY experiment, it is generally displayed as a 2-D contour plot. Figure 1.20 shows a HETCOR 2-D contour plot for the simple compound, butan-2-ol.

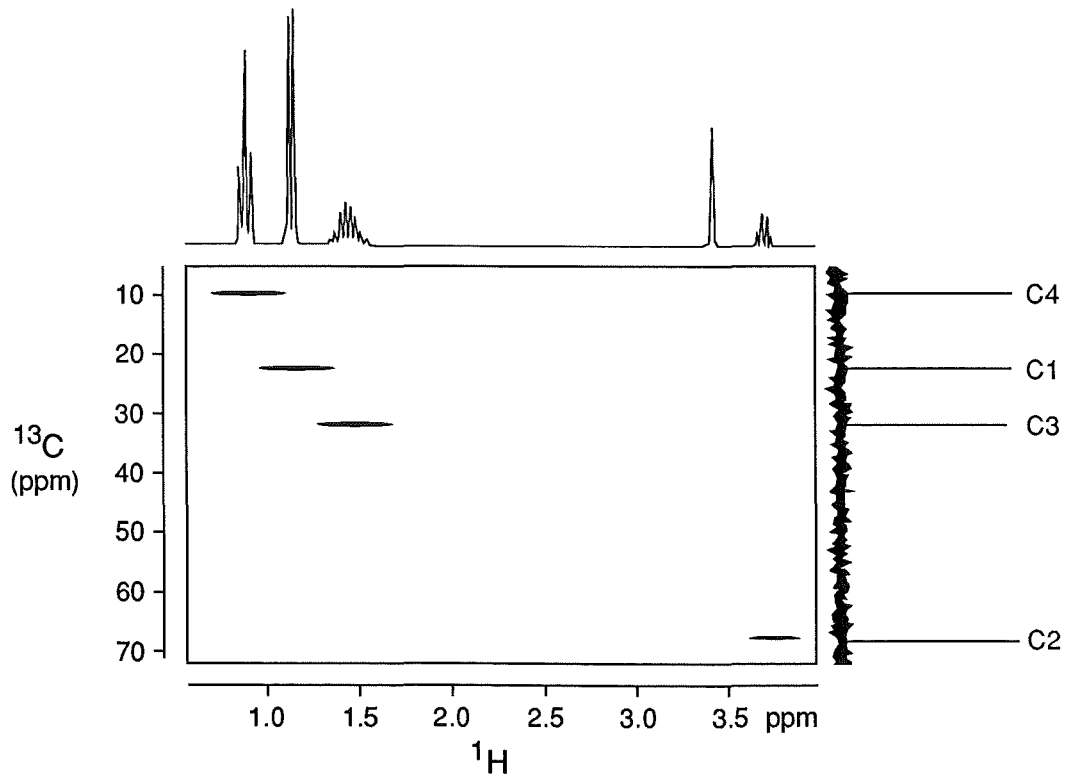


Figure 1.20 2-D contour plot showing the C-H correlations for butan-2-ol.

This experiment finds particular application in the assignment of n.m.r. signals, as it allows the signals for one type of nucleus (*e.g.* ^{13}C) to be assigned on the basis of the known assignment of the other (*e.g.* ^{1}H). One minor drawback of the technique is its relative insensitivity, requiring as a consequence reasonably large amounts of sample, although this problem has been alleviated to some extent, with the recent advent of "reverse detection" ^{1}H-^{13}C shift correlated experiments, involving ^{1}H detection.

The **XCORFE** (*X*-H *cor*relation with *f*ixed *e*volution time)[63] experiment involves the use of an indirect heteronuclear shift correlated pulse sequence, to enhance two and three bond C-H couplings, while simultaneously suppressing the single bond C-H couplings. This technique, offers an indirect means of obtaining C-C connectivities, thus allowing the establishment of the carbon skeletal framework of the compound. The power of this pulse sequence is ably demonstrated by McLean and Reynolds' use of the technique to determine the structure of the triterpenoid derivative, moretenone (122) (Figure 1.21).[64]

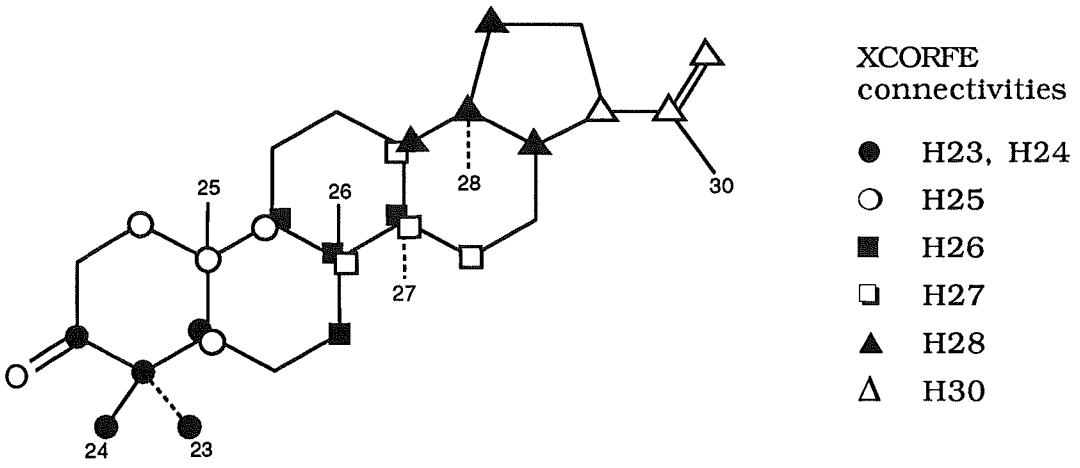


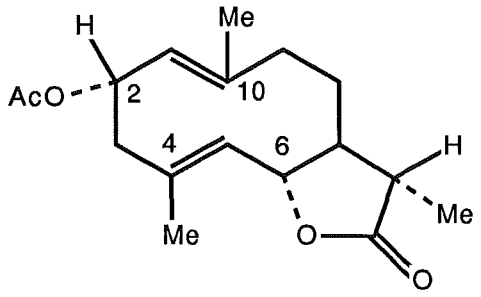
Figure 1.21 Results of XCORFE experiments on moretenone (122).

They found that the cross-correlations involving the methyl protons were particularly useful, as the methyl groups of the terpenoids are strategically located around the periphery of the molecule, and consequently provide a network of two and three bond connectivities, which effectively tie the molecule together. Figure 1.21 (above) summarizes some of the XCORFE correlations observed for moretenone.

The **INADEQUATE** (*I*ncredible *n*atural *a*bundance *d*ouble *qua*ntum *t*ransfer *e*xperiment)[65] is a 2-D pulse sequence which supplies a means for direct observation of C-C connectivities. Although this has obvious applications in structural assignment of the carbon skeletal framework of compounds, the inherent insensitivity of the technique precludes its use, unless very large amounts of the compound of interest are available. The XCORFE experiment (above) offers sensitivity far in excess of the INADEQUATE experiment, and is typically used as an alternative means of establishing the carbon framework.

Although the above mentioned techniques may yield extremely valuable information about homonuclear and heteronuclear coupling, and to some extent about the molecular framework, none of them supply information on the stereochemistry or conformation of molecules in solution.

Nuclear Overhauser effect (n.O.e.) difference spectroscopy, by revealing correlations between those nuclei coupled by dipole-dipole interactions, *i.e.* those nuclei located spatially close to one another, is able to provide important information on molecular configuration and conformation. The n.O.e. has been used as long ago as 1965[66] as an aid in organic structure elucidation, but it is only recently, with the advent of n.O.e difference spectroscopy[67] and 2-D n.O.e. spectroscopy (NOESY)[68] that the technique has become routinely available to the organic chemist. A typical example of the use of the n.O.e. was reported by Bhacca and Fischer[69] who used the technique to determine the molecular conformation of dihydro-tamaulipin-A acetate (123).



Compound (123)

Decoupler position	Enhancements observed
4-methyl	H6 (15%)
	H2 (10%)
	H1 (0%)
10-methyl	H2 (15%)
	H5 (0%)

Figure 1.22 N.O.e. correlations for dihydro-tamaulipin-A acetate (123).

Molecular model studies had indicated that the molecule could adopt conformations with the double bonds arranged either parallel, or

approximately perpendicular to one another. Because of the substitution at C4 and C10, this meant that a total of four different conformations were possible. The n.O.e. correlations observed for the acetate (123) are summarized in the Table above (Figure 1.22).

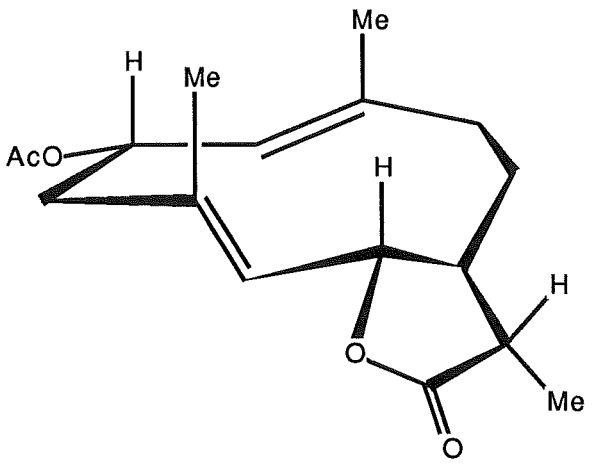


Figure 1.23 Conformation of compound (123).

The relatively large effects observed at H6 and H2, on irradiation of the 4-methyl resonance, implies that these spins must exist spatially close to one another, which in turn suggests an almost eclipsed relationship of these groups. The large effect between H2 and the 4- and 10-methyl groups similarly requires an eclipsed arrangement.

The results of these simple experiments allow the unambiguous assignment of the conformation of compound (123) in solution. A perspective diagram for this preferred conformation is presented in Figure 1.23 (above).

CHAPTER TWO

NITRATION OF CYCLOHEXA-2,4-DIENONES

2.1 INTRODUCTION

Section 1.3.3 presents a brief overview of the nitration reactions of phenols with nitrogen dioxide. The aim of the following introduction is to expand on this overview, concentrating in particular, on the reactions of 2,4,6-trialkyl phenols and their corresponding 4-nitrocyclohexa-2,5-dienones and 6-nitrocyclohexa-2,4-dienones with excess nitrogen dioxide.

2.1.1 Reactions of 2,4,6-trialkyl phenols with nitrogen dioxide

Reactions of 2,4,6-trialkyl phenols with excess nitrogen dioxide in non-polar media have been reported to yield either 2,5,6-trinitrocyclohex-3-enones,[46,51] or 4,5,6-trinitrocyclohex-2-enones[46,50] as major products, the reaction pathway followed in each case apparently being dependent on the relative sizes of the alkyl substituents.

2.1.1.1 Nitration of 2,6-di-*t*-butyl-4-methylphenol (201) with nitrogen dioxide in benzene[50] was found to proceed very slowly, yielding a small amount of a single 4,5,6-trinitrocyclohex-2-enone (203) (approximately 20% of the total product mixture). The major product of reaction was the 4-nitrocyclohexa-2,5-dienone (202). At the time, the results were interpreted in terms of the reaction scheme presented below (Figure 2.1). The 4-nitrodienone was suggested as the reaction intermediate, the trinitro ketone (203) arising from a subsequent slow addition of nitrogen dioxide to this dienone. Confirmation of the intermediacy of the 4-nitrodienone was obtained by recommitting the 4-nitrodienone to the reaction conditions: the final product mixture thus obtained was almost identical to that observed for reaction of the parent phenol.

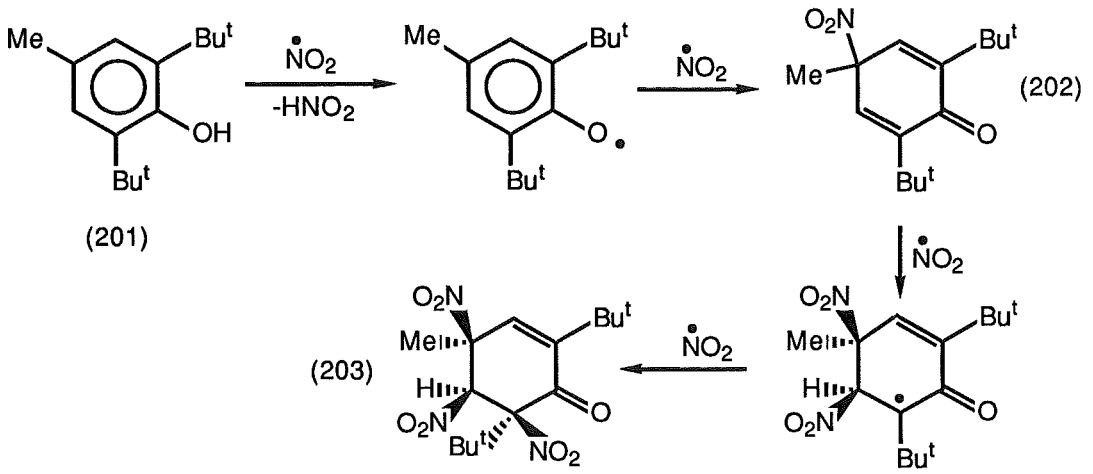


Figure 2.1 Reaction of 2,6-di-*t*-butyl-4-methylphenol with nitrogen dioxide. A proposed stepwise NO_2 addition to the 4-nitrodienone.

Despite the evidence for the intermediacy of the 4-nitrodienone, a recent ^{15}N labelling study on the reaction of the ^{15}N-labelled 4-nitrodienone,[70] revealed that the above reaction scheme is not followed. The trinitro ketone isolated from reaction of the labelled 4-nitrodienone was found to be labelled exclusively at C6, with no detectable amounts of ^{15}N label at either C4 or C5. This is not consistent with the above mechanism which would yield trinitro ketone labelled exclusively at C4. The revised reaction scheme, proposed to account for these recent observations, is presented in Figure 2.2 below. The 4-nitrodienone remains an intermediate in the reaction mechanism and its mode of formation is unchanged from the scheme above (these steps are therefore excluded from the reaction scheme below).

Homolysis of the ^{15}N-labelled 4-nitrodienone gives a labelled radical pair in a solvent cage, which by exchange of ^{15}N-nitrogen dioxide with the excess unlabelled nitrogen dioxide in the system can give the corresponding unlabelled radical pair. Recombination of these two radical pairs can then occur in two ways: (i) recombination with C4-N bond formation, yielding labelled and unlabelled 4-nitrodienone; and (ii) recombination with C6-N bond formation, yielding labelled and unlabelled 6-nitrodienone. Further reaction of the 6-nitrodienones with nitrogen dioxide yields the trinitro ketone (203), incompletely but exclusively labelled at C6. In terms of this reaction scheme, the slow rate of formation of the trinitro ketone (203) is seen as being due to a preference for recombination of the radical pairs to give the 4-nitrodienone, rather than to an inherently slow rate of addition of nitrogen dioxide to the 6-nitrodienone.

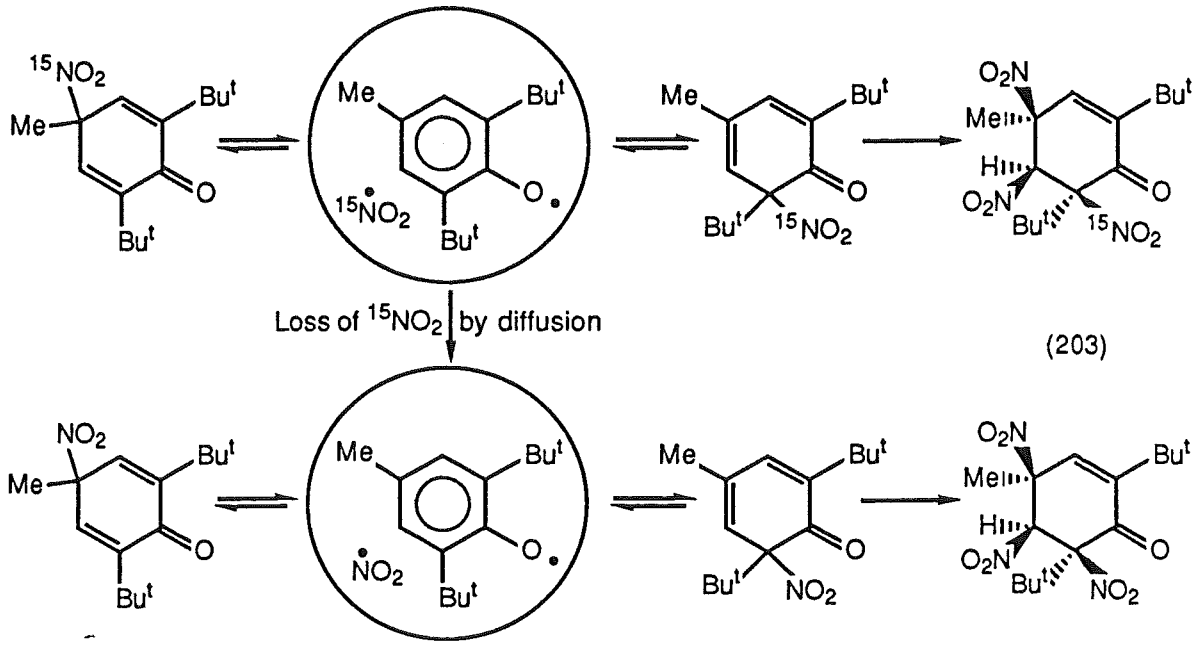


Figure 2.2 Proposed mechanism for the reaction of 2,6-di-*t*-butyl-4-methyl-4-nitrocyclohexa-2,5-dienone with nitrogen dioxide.

The formation of the trinitro ketone (203) is envisaged as occurring *via* a stepwise 4,5-addition of nitrogen dioxide to the 6-nitrodienone (204) (Figure 2.3). Initial attack by $\dot{N}O_2$ at C5 generates the delocalized radical (205), which undergoes a subsequent radical addition at the less hindered C4 position, to give the observed trinitro ketone (203).

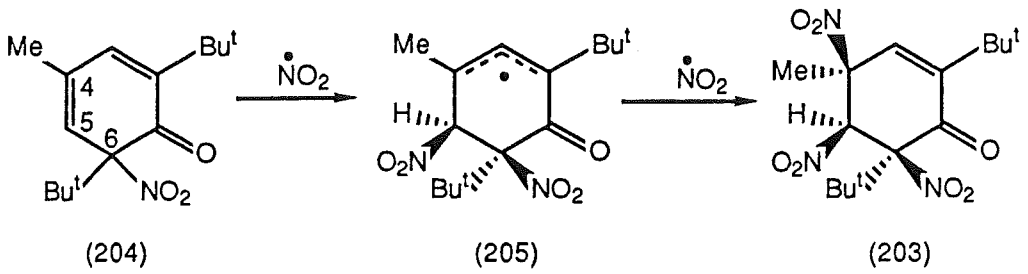
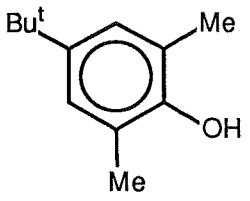


Figure 2.3 Stepwise 4,5-addition to a 6-nitrodienone.

2.1.1.2 The nitration reaction of 4-*t*-butyl-2,6-dimethylphenol (206) with nitrogen dioxide in benzene solution,[51] represents a complete contrast to the nitration of 2,6-di-*t*-butyl-4-methylphenol (201), discussed above.

Reaction with excess nitrogen dioxide is relatively rapid (the reaction proceeds to completion in under two hours), and the major products of reaction are the four epimeric 2,5,6-trinitrocyclohex-3-enones (210) (see Figure 2.4 below), although small amounts (total, approximately 15%) of the two C2-epimeric 6-hydroxy-2,5-dinitrocyclohex-3-enones (213) are also isolated.



Compound (206)

These observations were rationalized in terms of the reaction scheme below (Figure 2.4) [The 4-nitrodienone (207) is formed in an analogous manner to the previous 4-nitrodienone (202) (see Figure 2.1), and these steps are excluded from the following scheme]. The intermediacy of the 4-nitrodienone (207) in the reaction pathway was confirmed by committing a pure sample of the dienone to identical reaction conditions, the product mixture thus obtained being identical with that observed on nitration of the phenol (206).

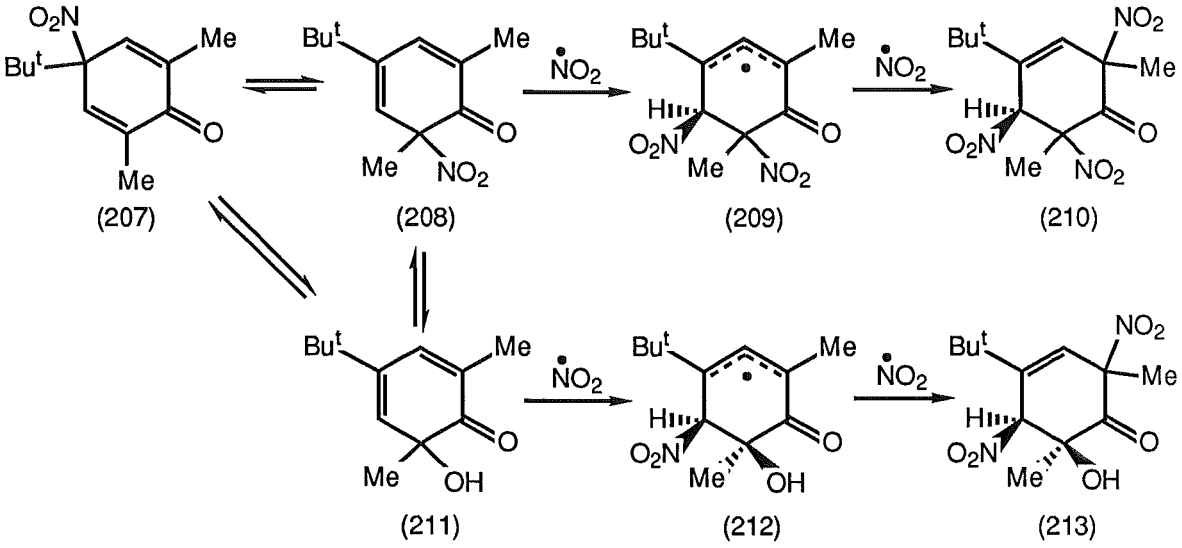


Figure 2.4 Proposed mechanism for the reaction of 4-di-*t*-butyl-2,6-dimethyl-4-nitrocyclohexa-2,5-dienone (207) with nitrogen dioxide.

The overall reaction scheme is closely similar to that proposed for the reaction of 2,6-di-*t*-butyl-4-methylphenol with nitrogen dioxide (see Figure 2.2), involving an equilibrium between the 4-nitrodienone and the corresponding 6-nitrocyclohexa-2,4-dienone, with a subsequent stepwise addition of nitrogen dioxide to this 6-nitrodienone. The large variations observed, in both the nature of the products formed and in the relative rates

of reaction, between the two phenols can be rationalized as effects due to the relative sizes of the alkyl substituents.

(i) The large difference in the relative rates of reaction can be correlated directly with the ease of formation of the 6-nitrodienone. In 4-*t*-butyl-2,6-dimethylphenol (206) the steric factors involved in forming the 6-nitrodienone (208) are minimal in comparison to those found for 2,6-di-*t*-butyl-4-methylphenol (201), where the large bulky *t*-butyl groups at C2 and C6 disfavour bond formation at C6, and thus the formation of the 6-nitrodienone (202). Because the reaction to final products, in both cases, occurs *via* the intermediacy of the 6-nitrodienones, the rate of reaction observed for 4-*t*-butyl-2,6-dimethylphenol (206) is far higher than that observed for 2,6-di-*t*-butyl-4-methylphenol (201).

(ii) The observation of cyclohex-3-enones (210) and (213) as the major reaction products in the nitration of 4-*t*-butyl-2,6-dimethylphenol (206), can also be rationalized by consideration of simple steric factors. Initial addition of nitrogen dioxide to the 6-nitrodienone (208) occurs at C5, giving the delocalized radical (209) (see Figure 2.4 above). At least in principle, this radical can undergo subsequent radical coupling with a further molecule of nitrogen dioxide at either C2 or C4. Here, coupling occurs exclusively at the less hindered C2-position, generating 2,5,6-trinitrocyclohex-3-enones (210).

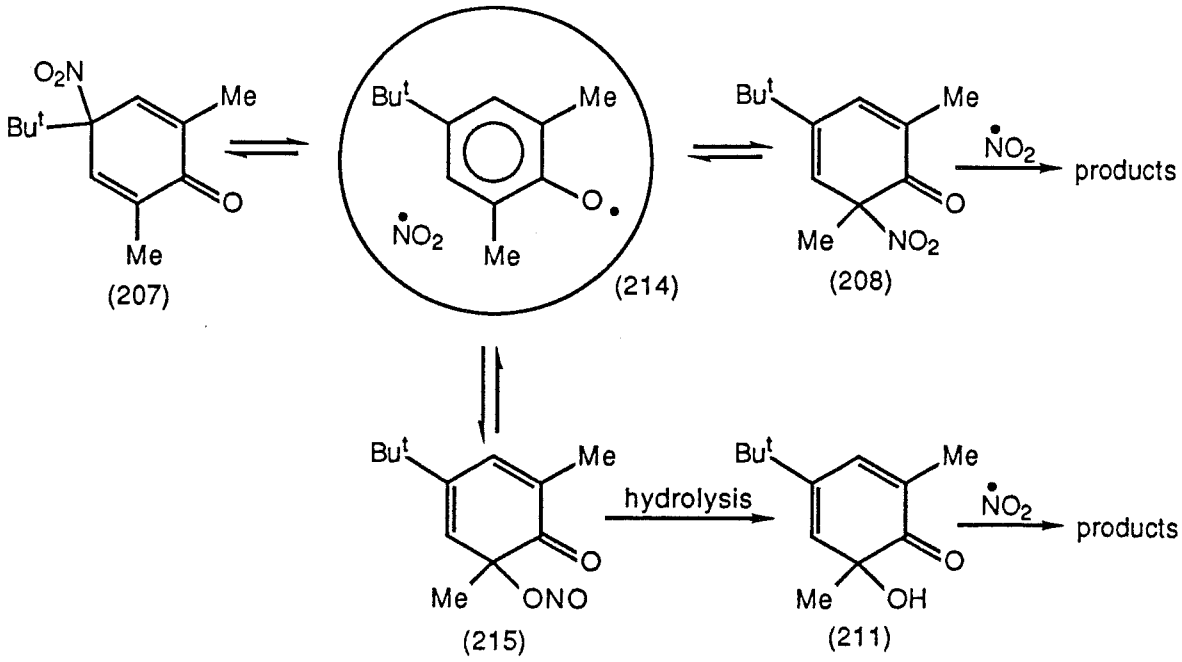
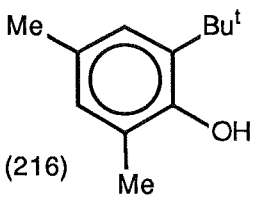


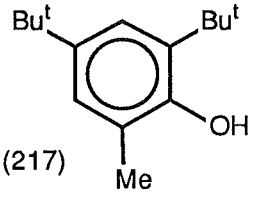
Figure 2.5 Proposed mechanism for the formation of the 6-hydroxydienone (211).

The two 6-hydroxy-2,5-dinitrocyclohex-3-enones (213) are envisaged as forming *via* an analogous stepwise 2,5-addition of nitrogen dioxide to the 6-hydroxydienone (211). This hydroxydienone probably forms by hydrolysis of the corresponding 6-nitritodienone (215), which could be expected to be formed by C6-O bond formation on collapse of the radical pair (214) (see Figure 2.5 above).

2.1.1.3 The reactions of the two 2,4,6-trialkyl phenols (216) and (217) with nitrogen dioxide have also been examined,[46] and in both cases the products observed can be readily rationalized in terms of the relative steric effects of the alkyl substituents (methyl *vs.* *t*-butyl) formulated for the two phenols discussed above (Sections 2.1.1.1 and 2.1.1.2). The reactions of the 4-nitrodienones of the above phenols with nitrogen dioxide have also been examined, and as before, they give identical reaction product mixtures with those obtained for the phenol, thus supporting their existence as reaction intermediates in the nitration reactions of the phenols.



(216)



(217)

Reaction of 2-*t*-butyl-4,6-dimethylphenol (216) with nitrogen dioxide in benzene yields only the two C4-epimeric cyclohex-2-enones (218) and (219) (Figure 2.6) as products of reaction.[46] These two trinitro ketones undoubtedly form *via* a reaction mechanism analogous to that presented in Figure 2.2 for the formation of the 4,5,6-trinitro ketones from 2,6-di-*t*-butyl-4-methylphenol (201): *i.e.* (i) generation of a 4-nitrodienone, (ii) equilibration with the corresponding 6-nitrodienone, and (iii) a subsequent stepwise 4,5-addition of nitrogen dioxide to this 6-nitrodienone.

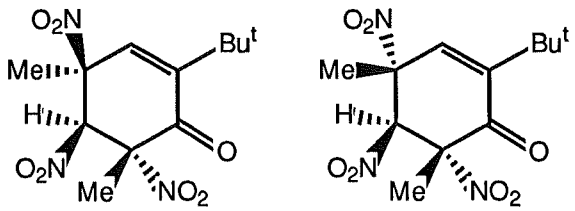
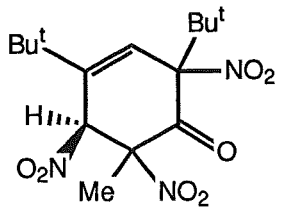


Figure 2.6

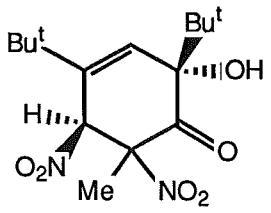
The two 4,5,6-trinitro ketones from nitration of 2-*t*-butyl-4,6-dimethylphenol. Compound (218) (left), and compound (219) (right).

Reaction of 2,4-di-*t*-butyl-6-methylphenol (217) with nitrogen dioxide in benzene solution proceeded to completion in 5 hours and yielded a mixture

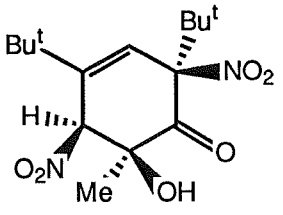
of seven cyclohex-3-enones, the four epimeric 2,5,6-trinitro ketones (220), the two C6-epimers (221), and a single 6-hydroxy-2,5-dinitrocyclohex-3-enone (222).



Compound (220)

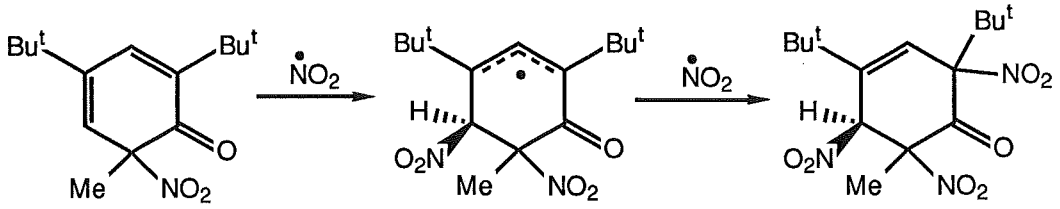


Compound (221)



Compound (222)

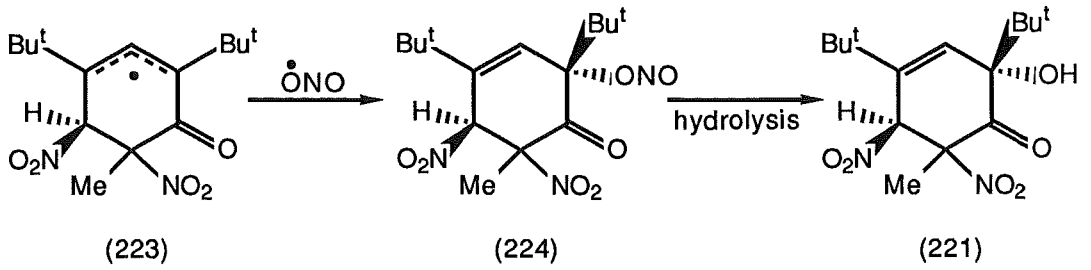
The modes of formation of these 2,5,6-trisubstituted products are exactly analogous to those postulated for the formation of the 2,5,6-trinitro ketones from 4-*t*-butyl-2,6-dimethylphenol (Figure 2.4, Section 2.1.1.2), although the exclusive generation of products with the 2,5,6-trisubstitution pattern is surprising (Figure 2.7, below).



(223) (220)

Figure 2.7 2,5-addition to 2,4-di-*t*-butyl-6-methyl-6-nitrocyclohexa-2,4-dienone.

Coupling of the delocalized radical (223) could occur at either C2 or C4, although in both cases approach of the nitrogen dioxide molecule would be hindered by the bulky *t*-butyl group. If steric factors were the sole factor in determining the site of nitrogen dioxide attack on this delocalized radical, then a mixture of 2,5,6- and 4,5,6-trinitro products could be expected. From the products isolated it is clear that attack occurs preferentially at C2, although the reason for this preference is uncertain. Furthermore, the isolation of the two C2-epimeric 2-hydroxy-2,5-dinitrocyclohex-3-enones demands that a second reaction possibility exists for reaction of the delocalized radical (223); namely reaction with $^{\bullet}$ONO followed by hydrolysis of the inferred 2-nitrito ketone (224) to give the corresponding hydroxy compound (221) (Figure 2.8).



(223) (224) (221)

Figure 2.8 Addition of an •ONO radical to the delocalized radical (223).

2.1.2 The dienone equilibrium

The labelling studies conducted on the ^{15}N-labelled 4-nitrodienones of 2,4,6-trialkyl phenols have established the transient intermediacy of 6-nitrodienones in the reactions of these phenols with nitrogen dioxide.[70,71,72] Furthermore, compelling evidence exists for the 4-nitrodienone also acting as an intermediate in these reactions. The 4-nitrodienones of all the 2,4,6-trialkyl phenols studied, react with nitrogen dioxide to yield product mixtures identical to those obtained from nitration of their parent phenols, and perhaps more significantly, the 4-nitrodienones can be isolated as products in short term reactions of the trialkyl phenols with nitrogen dioxide.

These facts are best rationalized in terms of a competing series of equilibria, as presented in Figure 2.9 below. The central feature of the scheme is the radical pair (226), the phenoxy radical having been formed *via* a hydrogen atom abstraction from the phenol. Combination of this radical pair can then occur in a number of different ways: (i) combination with C4-N bond formation to give the 4-nitrodienone (225) [equilibrium (a)], (ii) combination with C6-N bond formation to give the 6-nitrodienone (227) [equilibrium (b)], and (iii) combination with C6-O bond formation to give the 6-nitritodienone (228) [equilibrium (c)].

The characteristic reactions of 2,4,6-trialkyl phenols with nitrogen dioxide can now be rationalized in terms of the above competing set of equilibria.

(i) The observation of identical product mixtures, from independent reactions of the 4-nitrodienones and their corresponding parent phenols with nitrogen dioxide, is readily explained, as both reaction systems give rise to the same series of equilibria.

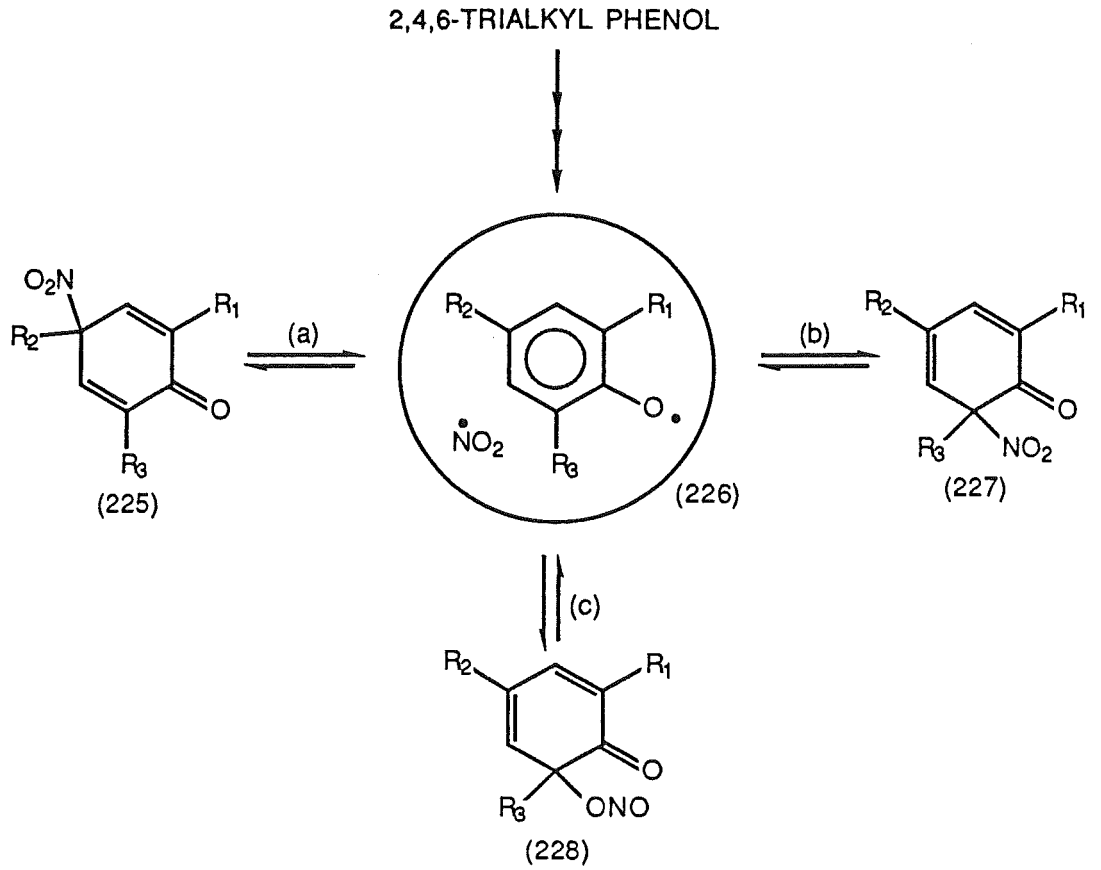


Figure 2.9 The "dienone equilibrium" established in the reaction of 2,4,6-trialkyl phenols with nitrogen dioxide.

(ii) The isolation of almost quantitative yields of 4-nitrodienones from short term reactions of the phenols with nitrogen dioxide, can be accounted for in terms of the relative crystallizability of the compounds constituting the equilibrium mixture. The 4-nitrodienones appear to crystallize readily, and given the equilibria observed above, the separation of crystalline 4-nitrodienone is not surprising.

(iii) The variation observed in the relative rates of reaction of the 2,4,6-trialkyl phenols with nitrogen dioxide can also be explained in terms of the equilibria (a), (b) and (c) in Figure 2.9. Because further reaction with nitrogen dioxide can occur only with cyclohexa-2,4-dienones (227) and (228), the relative amounts of these two species in solution will determine the overall rate of addition of nitrogen dioxide to give the final products. In the case of 2,6-di-*t*-butyl-4-methylphenol (201), the steric hindrance of the *t*-butyl groups at C2 and C6 result in a preference for combination of the radical pair (226) at C4, the concentrations of the 6-nitro and 6-nitrito dienones are thus relatively low, and addition product formation is slow.

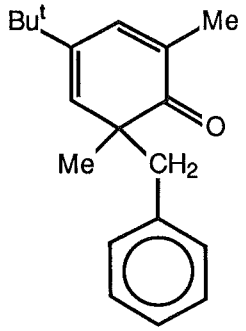
(iv) In this context, the observation that ^{15}N-labelled 4-nitrodienones react with nitrogen dioxide to yield trinitro ketones ^{15}N-labelled only at C6, points to the operation of the equilibrium between compounds (225) and (227), and to the inertness of the 4-nitrodienone (225) to direct addition of nitrogen dioxide.

2.1.3 The present work

The aim of this section of the present work was to synthesize some C6-substituted cyclohexa-2,4-dienone analogues of the postulated 6-nitro-dienone transient intermediate, and study their reactions with nitrogen dioxide.

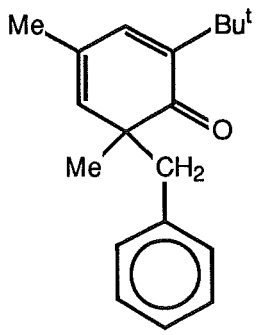
If indeed the 6-nitrodienone is the reactive intermediate in the nitration of 2,4,6 trialkyl phenols with nitrogen dioxide, then we would expect to see rapid reaction of the 6-nitrodienone analogues, yielding products with the same substitution patterns as those observed for the related phenol. Furthermore, the ratios of the various epimeric products isolated could be expected to be closely similar to the ratios observed in the parent phenol reactions.

The analogues chosen for study were the 6-benzylcyclohexa-2,4-dienones (229) and (230), formed by a C-alkylation of the parent phenol with benzyl chloride (see Experimental, Section 3.2). The 6-benzylcyclohexa-2,4-dienone analogue for the 6-nitrodienone of 4-*t*-butyl-2,6-dimethylphenol (206) is illustrated at right [compound (229)]. These 6-benzyldienones are stable, readily synthesized and purified, and most importantly, the benzyl group is inert to nitrogen dioxide attack (unlike an allyl group for instance), making them ideal substrates to study.



Compound (229)

The two particular 6-benzyldienones chosen for study were 6-benzyl-4-*t*-butyl-2,6-dimethylcyclohexa-2,4-dienone (229) (illustrated above), and 6-benzyl-2-*t*-butyl-4,6-dimethylcyclohexa-2,4-dienone (230) (shown below).



Compound (230)

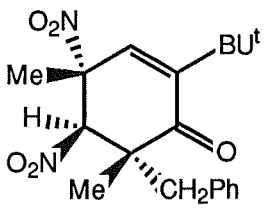
Compound (229) represents an analogue of those phenols with a comparatively small C2-substituent, and it should therefore give rise to predominantly 2,5-addition products with nitrogen dioxide. In contrast, the large C2-*t*-butyl group of compound (230) should offer sufficient steric hindrance at that position to prevent 2,5-addition reactions, and a stepwise 4,5-addition should be the predominant mode of reaction.

2.2 DISCUSSION

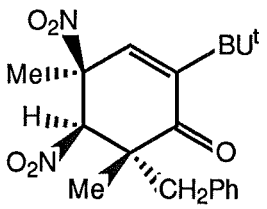
2.2.1 Reaction of 6-benzyl-2-*t*-butyl-4,6-dimethylcyclohexa-2,4-dienone (230) with nitrogen dioxide

Reaction of the cyclohexa-2,4-dienone (230) with excess nitrogen dioxide in benzene solution gave a crude product which was shown (^{1}H n.m.r.) to be a mixture (*c.* 40:23:8:8:7:6:3:1) of two major [compounds (232) and (231)] and a number of minor [compounds (234), (236), (235), (233), (237) and (238)] components. These components were generally separated by chromatography on silica, using a Chromatotron, although two compounds, (234) and (235), required further purification by h.p.l.c. The percentage yields quoted below, and in the Experimental Section, were estimated from the respective integrals in the ^{1}H n.m.r. spectrum of the crude product mixture, and do not reflect the amount of pure material isolated.

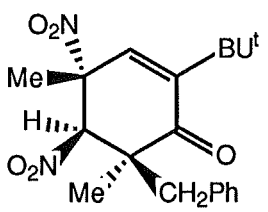
2.2.1.1 The four possible stereoisomers (*d*-, *l*- pairs) with the 4,5-dinitrocyclohex-2-enone structure were eluted from the silica gel plate in the elution order: compound (233) (6%), compound (231) (23%), compound (232) (40%), and compound (234) (8%).



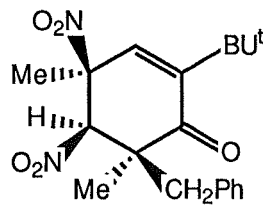
Compound (231)



Compound (232)



Compound (233)



Compound (234)

The structural assignments for the dinitro ketones (231), (232), (233) and (234) are based on (i) the single crystal X-ray structure analyses performed for compounds (231) and (232), (ii) the general similarity of the spectroscopic data for the four compounds, (iii) results from selected nuclear Overhauser effect (n.O.e.) experiments, and (iv) the correlation, developed below, between the relative 4,5-dinitro group stereochemistry and the ^{1}H n.m.r. chemical shifts of the adjacent H3 and H5 protons.

A perspective drawing of *c*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-4,*t*-5-dinitrocyclohex-2-enone (231) is presented in Figure 2.10 (corresponding atomic coordinates are given in Section 3.3, Table 1).

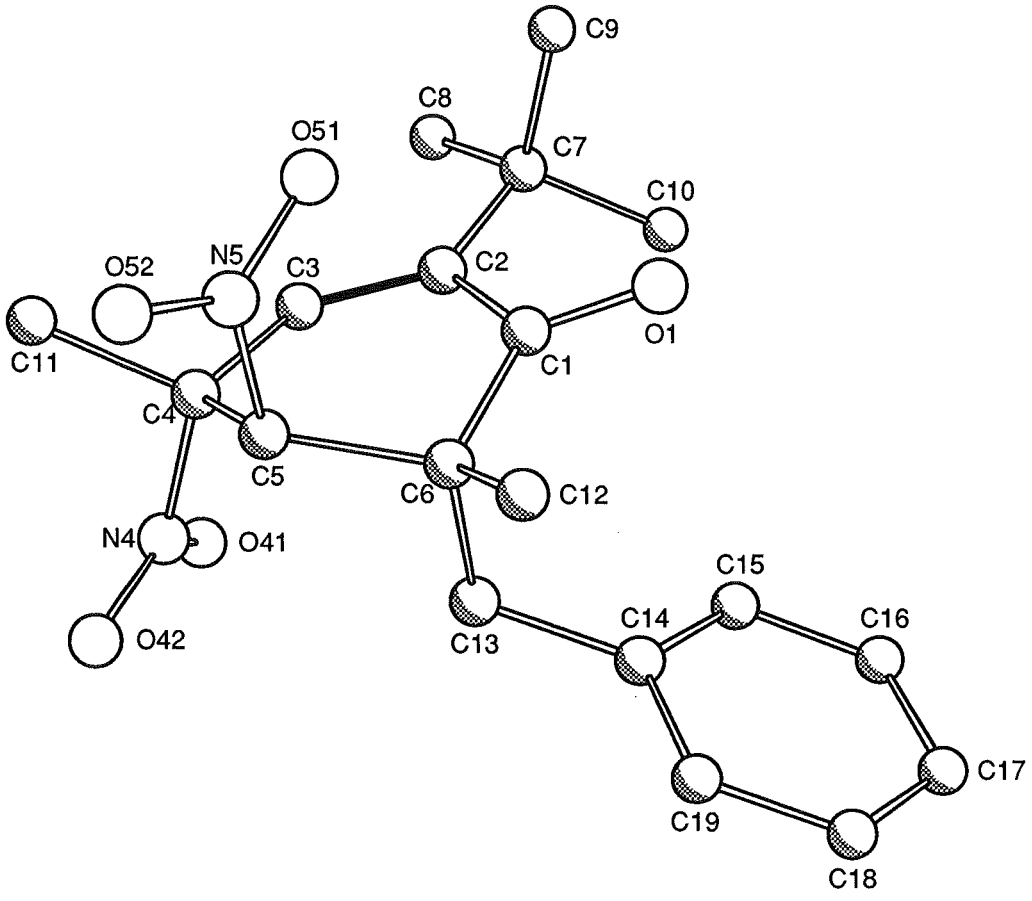


Figure 2.10 Perspective diagram of compound (231). Double bond shown in black.

Similarly, a perspective drawing of *t*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-4,*c*-5-dinitrocyclohex-2-enone (232) is presented in Figure 2.11 (corresponding atomic coordinates: Section 3.3, Table 2).

In the solid state both compounds, (231) and (232), exist with the alicyclic ring in a slightly flattened half chair conformation (C1, sp^{2}) with the 5-nitro

and 6-benzyl groups in axial orientations [torsional angles: for compound (231), N5-C5-C6-C13 174.9(3)°; for enantiomer of compound (232), 167.7(3)°]. The conformation adopted by the benzyl group is similar in the two compounds [torsional angles: for (231), C6-C13-C14-C15 -90.2(5)°, C5-C6-C13-C14 -170.4(4)°; for enantiomer of (232) -86.8(5)° and -163.4(3)° respectively].

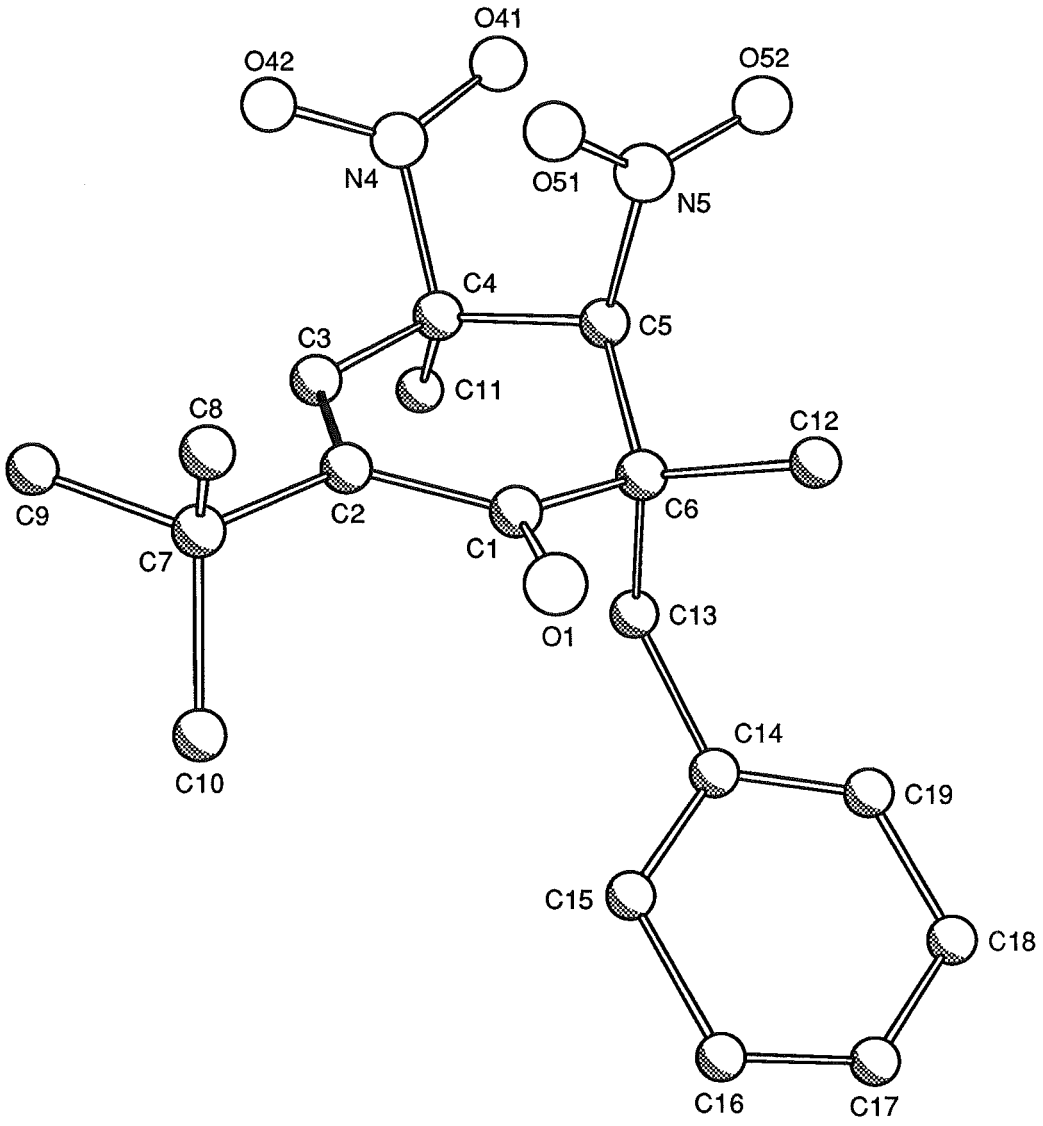


Figure 2.11 Perspective diagram of compound (232). Double bond shown in black.

In both compounds the plane of the axial 5-nitro group is close to being eclipsed with the C5-H5 bond [torsional angles: for (231), H5-C5-N5-O52 -8.4(5)°; for (232), H5-C5-N5-O52 -15.8(3)°]. In the *trans*-dinitro compound (231) the 4-nitro group occupies the *pseudo*-axial position, whereas the 4-nitro group is *pseudo*-equatorial in the *cis*-dinitro compound (232). For the compounds (231) and (232), the plane of the 5-nitro group

is close to perpendicular to the C4-C11 bond [torsional angles: for (231), C11-C4-N4-O41 104.3(4)°; for enantiomer of (232) 86.0(4)°].

Comparison of the n.m.r. solution spectra of the two epimers, (231) and (232), allows further structural comment to be made. First, selected n.O.e. experiments conducted on the two compounds were consistent with the structures in the solid state, determined above. While no n.O.e. enhancement of the 4-methyl (C11) signal for compound (231) was observed on irradiation of either the 6-methyl (C12) or the 6-methylene (C13) protons, corresponding experiments for compound (232) resulted in an enhancement (2%) of the 4-methyl (C11) signal on irradiation of the 6-methylene (C13) protons, although no effect on the 4-methyl signal was observed on irradiation of the 6-methyl (C12) protons.

The magnitude of the 4-methyl/ 6-methylene n.O.e. enhancement observed in compound (232) can be rationalized by simple inspection of Figure 2.12, and is in keeping with the stereochemical relationship of the two groups in the solid state, established above (Figure 2.11).

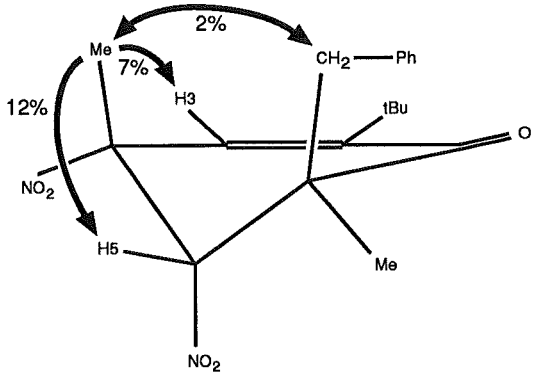


Figure 2.12
N.O.e. enhancements for compound (232).

Second, comparison of the ^{1}H n.m.r. chemical shifts of H3 and H5 for the two C4-epimeric compounds (231) and (232), reveals that the C4-stereochemistry has a pronounced effect on the chemical shifts of the H3 and H5 atoms. The chemical shifts for the *trans*-dinitro compound (231) are δ 6.60 ppm (H3) and δ 5.84 ppm (H5), but for the *cis*-dinitro compound (232) the signal for H3 occurs relatively further downfield at δ 6.87 ppm (Δ 0.27 ppm) and the signal for H5 occurs relatively markedly upfield at δ 5.35 ppm (Δ -0.49 ppm). These results parallel the trend observed for the ^{1}H n.m.r. chemical shifts of the H3 proton for the two C4-epimers (218) and (219), formed in the nitration of 2-*t*-butyl-4,6-dimethylphenol (216) (see Section 2.1.1.3). The *trans*-dinitro compound (219) displays resonances at δ 6.53 ppm (H3) and δ 6.97 ppm (H5), whereas the corresponding resonances for the *cis*-dinitro compound (218) appear at δ 6.74 ppm (Δ 0.21 ppm) and δ 6.11 ppm (Δ -0.86 ppm) respectively.

If the assumption is made that the conformations of compounds (231) and (232) in the solid state, are approximately similar to those in solution, then the above chemical shift trends can be rationalized. In compound (231) the 4-nitro group occupies a *pseudo*-axial position (Figure 2.10), and as a consequence the deshielding experienced by H5 due to this nitro group is relatively high in comparison to that encountered in compound (232), where the 4-nitro group is in a *pseudo*-equatorial position. This increased deshielding of H5 in (231) results in an H5 resonance further downfield than the H5 resonance of compound (232). Similarly, the greater deshielding, by the 4-nitro group of H3 in compound (232) due to their relative proximity (Figures 2.11 and 2.12), means the H3 resonance in the ^{1}H n.m.r. spectrum of compound (232) is further downfield than the corresponding resonance for compound (231).

The remaining two 4,5-dinitrocyclohex-2-enones were assigned structures (233) and (234). The general spectroscopic data pointed to these compounds being stereoisomers of the dinitro ketones (231) and (232), the structures of which have been established by X-ray analyses above.

Examination of the ^{1}H n.m.r. spectroscopic data for compounds (233) and (234) allow their stereochemistry to be assigned. For the *cis*-dinitro compound (234), irradiation of the 6-methyl protons resulted in a n.O.e. enhancement (5%) of the 4-methyl signal, but irradiation of the 6-methylene protons had no effect on the 4-methyl signal (Figure 2.13).

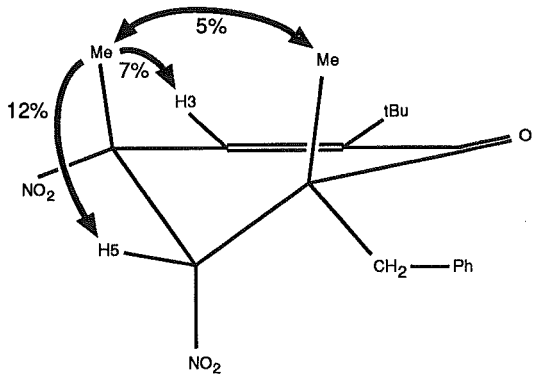


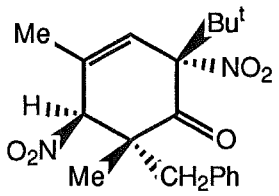
Figure 2.13
N.O.e. enhancements for compound (234).

These results indicate that the 4-methyl and 6-methyl groups have a *syn-pseudo*-axial/axial relationship on the alicyclic ring system of compound (234), as this is the only conformation which allows sufficient proximity for a significant n.O.e. correlation to be observed between these two groups. For the *trans*-dinitro compound (233), irradiation of either the 6-methyl or the 6-methylene protons has no effect on the 4-methyl signal, indicating that in this case the 4-methyl group occupies a *pseudo*-equatorial position. This is in accord with the assigned stereochemistry.

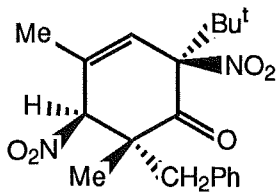
Following the large shifts observed in the ^{1}H n.m.r. chemical shift values of H3 and H5 for compounds (231) and (232) (see discussion above), an effect of their differing C4-stereochemistry, a similar comparison of the relative ^{1}H n.m.r. chemical shift data for the H3 and H5 protons in compounds (233) and (234) was made. This comparison provides further support for the stereochemical assignment made above. For the *trans*-dinitro compound (233) the ^{1}H n.m.r. signals for H3 and H5 occur at δ 6.48 ppm and δ 5.72 ppm respectively, while the corresponding signals for the *cis*-dinitro compound appear at δ 6.71 ppm (H3) and δ 5.37 ppm (H5). Thus, relative to the ^{1}H n.m.r. data for the *trans*-dinitro compound (233), the H3 signal for the *cis*-dinitro compound (234) occurs downfield (Δ 0.23 ppm), while the H5 signal appears upfield (Δ -0.35 ppm); these trends parallel those observed for the C4-epimers (231) and (232), the structures of which have been established above, and hence provide support for the stereochemical assignments for compounds (233) and (234).

In comparing the elution order from a Chromatotron silica gel plate of the four 4,5-dinitrocyclohex-2-enones (231), (232), (233) and (234), it is of interest to note that, for a given C6-stereochemistry, the *trans*-dinitro isomer (231) or (233) is eluted ahead of the *cis*-dinitro isomer (232) or (234). This parallels earlier observations of the elution order of stereoisomeric 2,5,6-trinitrocyclohex-3-enones where, for a given C6-stereochemistry, *trans*-2,5-dinitro compounds are eluted ahead of their *cis*-2,5-dinitro isomers.[46]

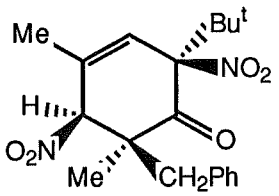
2.2.1.2 Three of the four possible stereoisomers (*d*- , *l*- pairs) with the 2,5-dinitrocyclohex-3-enone structure were eluted from the silica gel Chromatotron plate in the order: compound (235) (7%), compound (236) (8%) and compound (237) (3%).



Compound (235)



Compound (236)



Compound (237)

The structural assignments of the dinitro ketones (235), (236), and (237) are based on (i) the X-ray structure determinations for compounds (235)

and (236), (ii) the general similarity of the spectroscopic data for the three compounds, and (iii) results of selected n.O.e. difference experiments.

A perspective drawing of *c*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (235) is presented in Figure 2.14 (corresponding atomic coordinates are given in Section 3.3, Table 3).

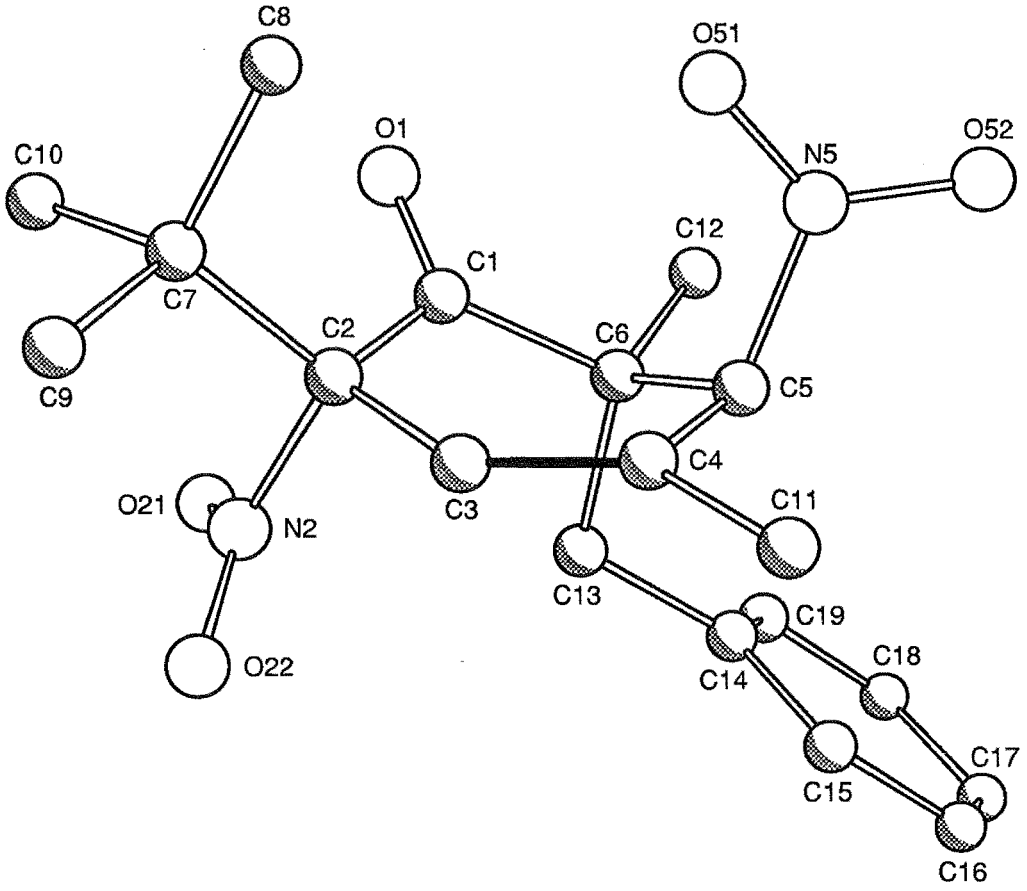


Figure 2.14 Perspective diagram of compound (235). Double bond shown in black.

Similarly a perspective diagram for *t*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (236) is presented in Figure 2.16 (corresponding atomic coordinates are given in Section 3.3, Table 4). For each compound, (235) and (236), the structure consists of two, well-separated, crystallographically independent molecules; superposition of the two independent molecules (Figure 2.15), in each case, revealed no gross differences of any chemical significance.

In the solid state the two 2,5-dinitro compounds (235) and (236) exist with the alicyclic ring in markedly different conformations. While the alicyclic ring of the *trans*-dinitro compound (235) exists in a much distorted half

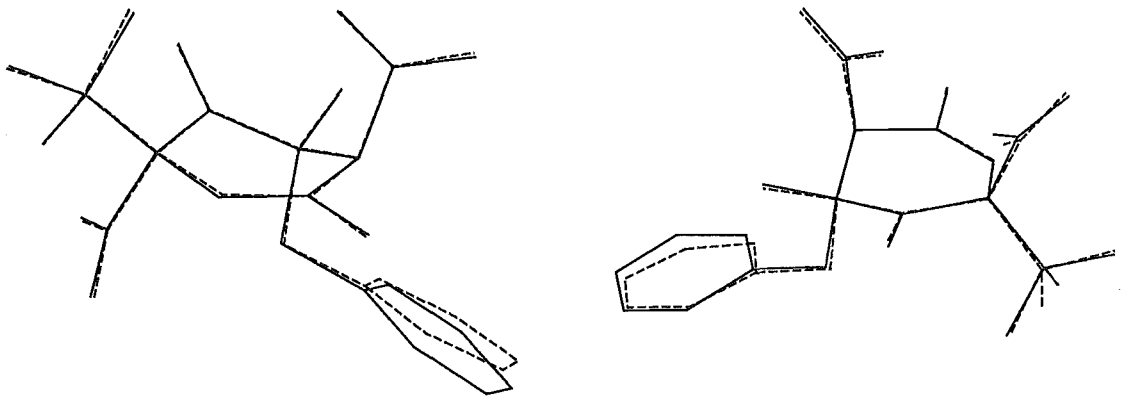


Figure 2.15 Superpositions of the two crystallographically independent molecules. Compound (235) (left), and compound (236) (right).

chair conformation [*e.g.* torsional angles for molecule 1: C1-C2-C3-C4 -0.3 (5)°; C3-C4-C5-C6 -18.9(5)°], the alicyclic ring of the *cis*-dinitro compound (236) exists as a skew boat [*e.g.* torsional angles for molecule 1: C1-C2-C3-C4 18.6(6)°; C3-C4-C5-C6 -29.6(6)°]. A similar pattern of alicyclic ring conformations was observed for three of the stereoisomers of the 2,4-di-*t*-butyl-6-methyl-2,5,6-trinitrocyclohex-3-enones (220), with the two *cis*-2,5-dinitro compounds existing in skew boat conformations and one of the *trans*-2,5-dinitro compounds in a flattened half chair conformation.[46]

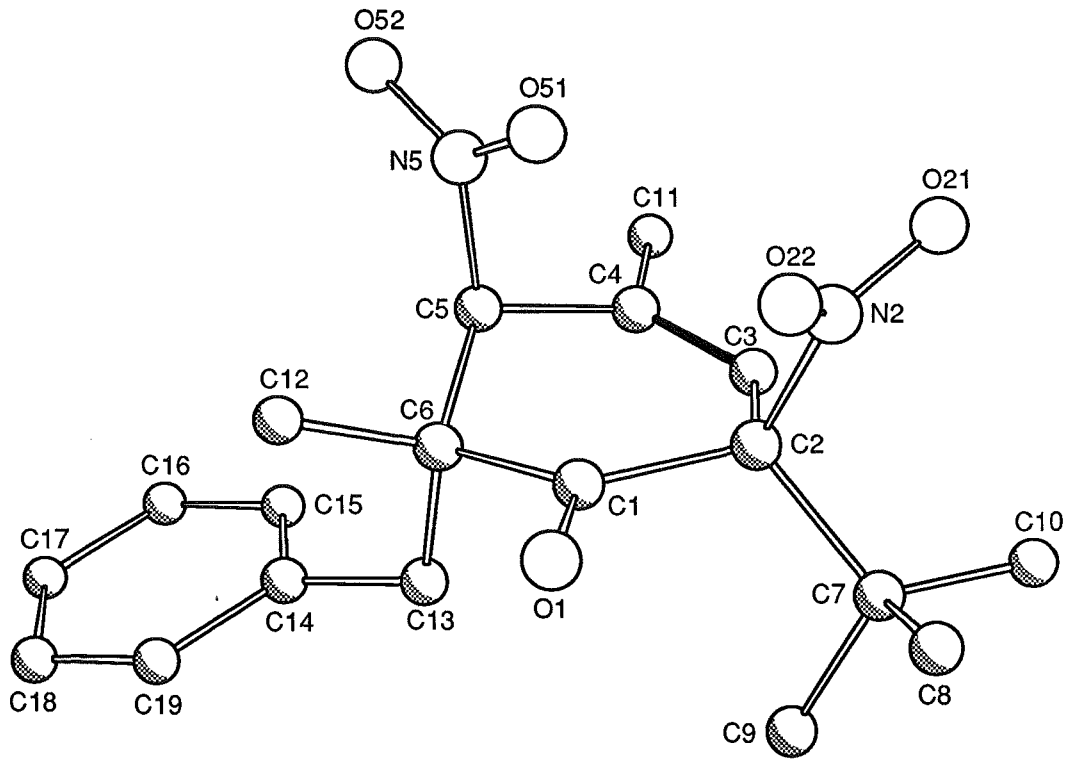


Figure 2.16 Perspective diagram of compound (236). Double bond shown in black.

This conformational difference presumably arises from the non-bonding interaction between the bulky 2-*t*-butyl group and the *syn* substituent at C6 [*e.g.* C13 in compound (236)] which must be accommodated in such *cis*-2,5-dinitro compounds. In the solid state both compounds (235) and (236) exist in conformations in which (i) the plane of the 5-nitro group is close to eclipsed with the C5-H bond [*e.g.* torsional angles for molecule 1: H5-C5-N5-O52 1.2(4)° for (235); -9.1(4) for (236)], (ii) the plane of the 2-nitro group is at approximately 90° to the C2-C7 bond, (iii) the 5-nitro and 6-methylene groups are in the *anti* relationship, (iv) the phenyl ring lies at approximately 90° to the C6-C13 bond, and (v) the C6-C1 and the C13-C14 bonds are in the *anti* relationship.

The spectroscopic data for compounds (235) and (236) were in accord with the established structures. For compound (236) irradiation of the *t*-butyl protons resulted in a n.O.e. enhancement (8%) of the downfield proton of the 6-methylene group, consistent with their proximate *syn* relationship (Figure 2.17).

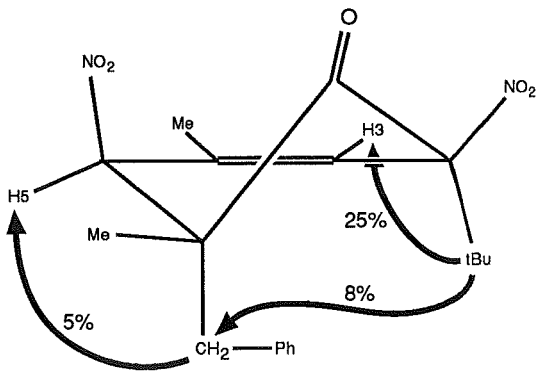


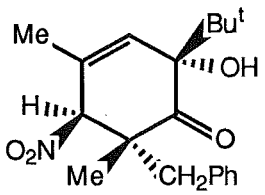
Figure 2.17
N.O.e. enhancements for compound (236).

In contrast, irradiation of the *t*-butyl protons of compound (235) resulted in no observable n.O.e. enhancement of either the 6-methylene or the 6-methyl protons.

The stereochemistry of compound (237) was established as follows. First, and by exclusion, its structure must contain the *trans* 6-methyl/5-nitro structural feature, as both the 2,5-dinitro ketones containing the *cis* 6-methyl/5-nitro structural feature had already been isolated and identified [compounds (235) and (236) above]. Second, irradiation of the *t*-butyl protons of this compound (237) resulted in a n.O.e. enhancement (2%) of the 6-methyl proton signal, consistent with a *syn* relationship of these two groups. These two facts demand a structure analogous to that for compound (236), except that the 6-benzyl and 6-methyl groups are interchanged.

2.2.1.3 The gross structure of the 2-hydroxy-5-nitrocyclohex-3-enone (238) is supported by its spectroscopic data and its molecular formula (from

high resolution mass spectrometry). The absence of an observable n.O.e. enhancement of the signals due to either the 6-methyl or the 6-methylene protons on irradiation of the *t*-butyl protons suggests that the *t*-butyl group is *cis* to the 5-nitro group, a group which characteristically occupies either the *pseudo*-axial or flagpole orientation on a cyclohex-3-enone ring system.



Compound (238)

The assignment of the C6-stereochemistry rests upon a comparison of the n.O.e. enhancements observed for the signal due to H5, on irradiation of the 6-methylene or 6-methyl protons. For the three compounds (235), (236) and (238), two of which have already been demonstrated as having the *cis* 5-nitro/6-methyl relationship (see Section 2.2.1.2 above), irradiation of the 6-methylene protons leads to a n.O.e. enhancement of the signal due to the H5 proton of 5-6%, and irradiation of the 6-methyl protons leads to a H5 signal enhancement of 6-7%. In contrast, for compound (237) which is known to have the *trans* 5-nitro/6-methyl relationship (see Section 2.2.1.2), irradiation of the 6-methylene protons leads to a n.O.e. enhancement of the H5 proton signal of only 1%, and irradiation of the 6-methyl protons leads to a H5 signal enhancement of 9%.

These effects can be rationalized by consideration of selected torsional angles from the single crystal X-ray structure analyses performed on compounds (235) and (236). These torsional angles reveal that for those compounds with a *cis* relationship between the 5-nitro and 6-methyl groups, the H5 hydrogen atom is far from being perfectly staggered with respect to the substituents at C6 (Figure 2.18).

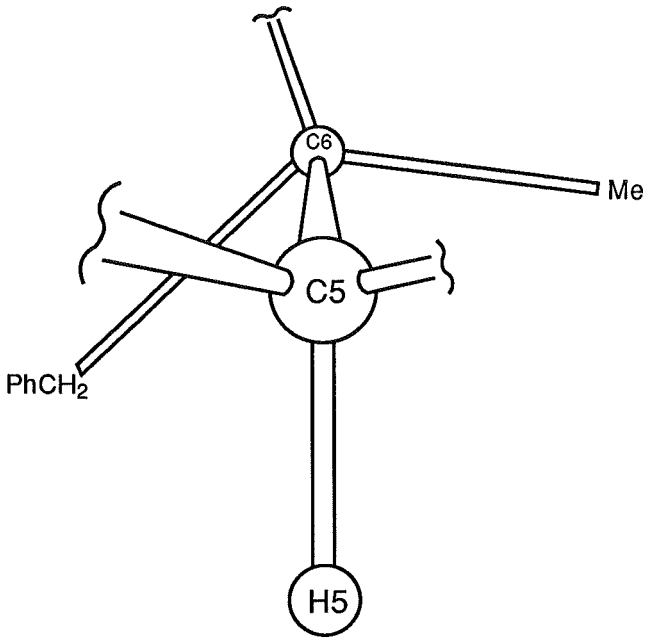
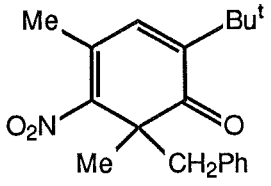


Figure 2.18 Structural fragment from compounds (235) and (236).

Indeed, the benzyl group lies significantly closer to the plane of the C5-H5 bond [*e.g.* torsional angles for molecule 1: C13-C6-C5-H5 45.0(3)° for compound (235), 45.5(3)° for compound (236)] than does the C6-methyl group [*e.g.* torsional angles for molecule 1: C12-C6-C5-H5 -77.2(3)° for compound (235), -75.8(3)° for compound (236)]. Despite this conformational preference, the magnitude of the n.O.e. correlations between H5 and the methylene group, and H5 and the C6-methyl group are closely similar. If the assumption is made that altering the C6-stereochemistry will not markedly alter the alicyclic ring conformation, then such an alteration should be reflected in a change in the relative magnitudes of the above n.O.e. enhancements: *i.e.* a somewhat larger effect between the C6-methyl group and H5, and a somewhat smaller effect between the methylene protons and H5. This is exactly what is observed for the *trans* 5-nitro/6-methyl compound (237).

Compound (238) displays n.O.e. correlations very similar to compounds (235) and (236) [separate irradiations of the 6-methyl and 6-methylene signals for compound (238) both gave enhancements of the H5 signal of *c.* 6%] and is seen therefore as having a *cis* 5-nitro/6-methyl relationship, and being related to compound (235) by a simple replacement of the 2-nitro group of the latter by a hydroxy group.

2.2.1.4 A further compound (239) was isolated from the chromatographic separation of the products of reaction of nitrogen dioxide with dienone (230). This compound (239) was not present in the mixture prior to chromatography and is believed to be a decomposition product derived from the genuine reaction products. The structure of this material, which could be isolated only in low yield, is based on its molecular formula (mass spectrometry) and its general spectroscopic data.

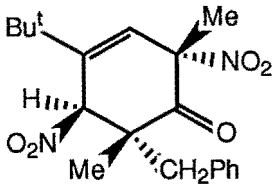


Compound (239)

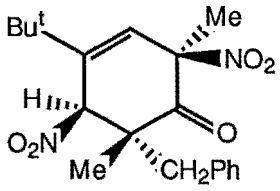
2.2.2 Reaction of 6-benzyl-4-*t*-butyl-2,6-dimethylcyclohexa-2,4-dienone (229) with nitrogen dioxide

Reaction of the cyclohexa-2,4-dienone (229) with nitrogen dioxide in benzene solution gave a crude product which was shown (^{1}H n.m.r.) to be a mixture (c. 57:32:4:2:2:1:1) of two major [compounds (241) and (240)] and a number of minor [compounds (242), (243), (244), (245) and (246)] components. These components were separated by chromatography on silica, using a Chromatotron. The yields quoted below, and in the Experimental Section, were estimated from the ^{1}H n.m.r. spectrum of the crude product and do not reflect the amount of pure material isolated.

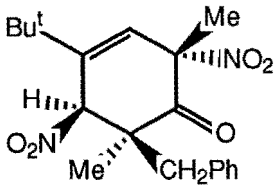
2.2.2.1 The four possible stereoisomers (*d*-, *l*- pairs) with the 2,5-dinitrocyclohex-3-enone gross structure were eluted from the silica gel plate in the elution order: compound (242) (4%), compound (240) (32%), compound (241) (57%) and compound (243) (2%).



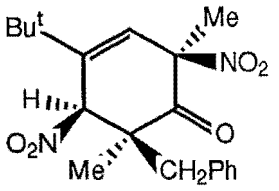
Compound (240)



Compound (241)



Compound (242)



Compound (243)

The structural assignments for dinitro ketones (240), (241), (242) and (243) are based on (i) the single crystal X-ray structure analysis for compound (240), (ii) the general similarity of the spectroscopic data for the four compounds, (iii) results from selected n.O.e. difference experiments, and (iv) the known correlation between the ^{1}H n.m.r. chemical shift of the H3 proton and the relative stereochemistry of the two nitro groups at C2 and C5.[73]

A perspective drawing of *c*-6-benzyl-4-*t*-butyl-2,6-dimethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (240) is presented in Figure 2.19 (corresponding atomic coordinates are given in Section 3.3, Table 5). In the solid state the *trans*-dinitro compound (240) exists with the alicyclic ring in a skew boat conformation [torsional angles: C1-C2-C3-C4 -11.4(5)°, C3-C4-C5-C6 35.7(5)°] with the 5-nitro group in the flagpole orientation.

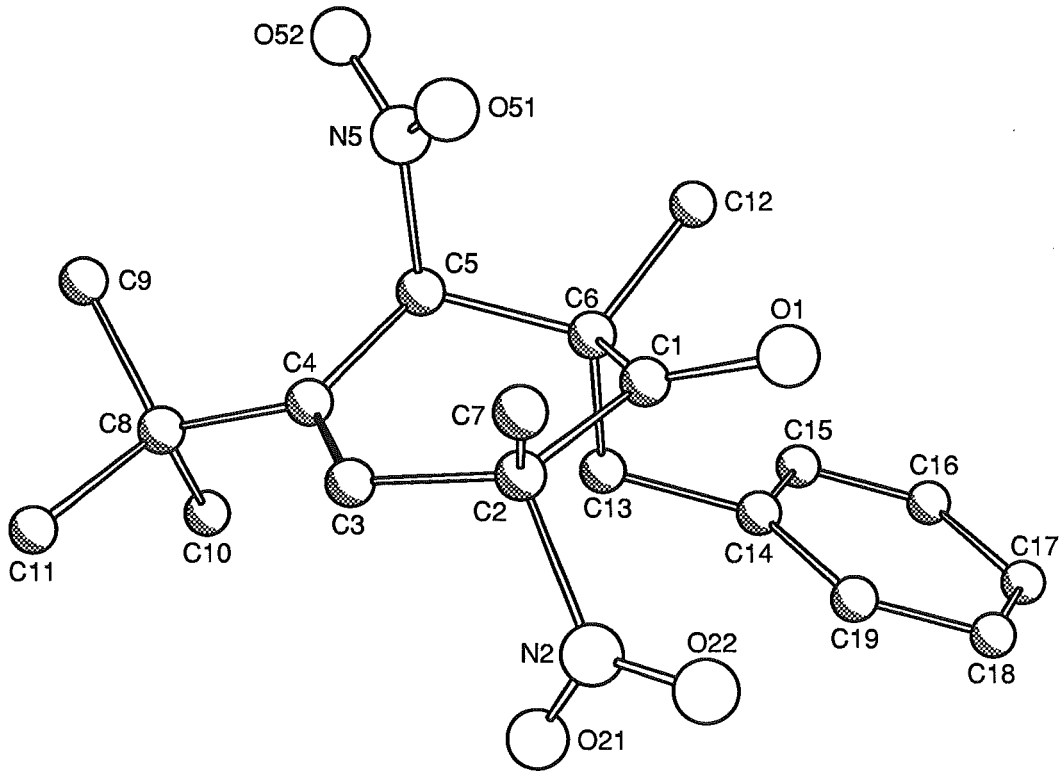


Figure 2.19 Perspective drawing of compound (240). Double bond shown in black.

The plane of the 5-nitro group is close to being eclipsed with the C5-H5 bond [torsional angle: H5-C5-N5-O52 6.2(3)°], and the 5-nitro and 6-benzyl groups exist in an *anti* relationship as indicated by the torsional angle: N5-C5-C6-C13 -170.8(2)°. Selected n.O.e. difference experiments revealed an enhancement (7%) of the signal due to the H3 proton on irradiation of the 2-methyl (C7) protons, but the signals due to the 6-methyl (C12) and 6-methylene (C13) protons were not affected, in keeping with the established structure of compound (240).

The spectroscopic data for the four isomeric 2,5-dinitrocyclohex-3-enones (240), (241), (242) and (243), were consistent with the structures assigned to them. The stereochemical assignment for each of these compounds is based on a consideration of their respective n.m.r. spectroscopic data. In this respect, n.O.e. experiments proved of enormous value. Irradiation of the 2-methyl protons of the *trans*-dinitro compound (242) resulted only in a n.O.e. enhancement (6%) of the signal due to the H3 proton, and the signals due to the 6-methyl and 6-methylene protons were not affected. This absence of any significant n.O.e. correlation between the 2-methyl group and the C6-substituents indicates that the 2-methyl group occupies a *pseudo*-equatorial position, *cis* to the 5-nitro group, a group which

characteristically occupies either the *pseudo*-axial or flagpole orientation on a cyclohex-3-enone ring system. Given the established structure for the other *trans*-dinitro compound (240), above, by exclusion the second *trans*-dinitro compound must have the stereochemistry (242).

The stereochemistry of the two *cis*-dinitro compounds (241) and (243) were determined on the basis of results obtained from further n.O.e. experiments. Irradiation of the 2-methyl protons of compound (241) resulted in a n.O.e. enhancement (2%, downfield proton; 1%, upfield proton) of the AB quartet due to the 6-methylene protons, but the signal due to the 6-methyl protons was not affected. In contrast, irradiation of the 2-methyl protons of compound (243) resulted in a n.O.e. enhancement (2%) of the signal due to the 6-methyl protons, and the signal due to the 6-methylene protons was not affected. These enhancements can be readily explained in terms of a cross-ring n.O.e. correlation (Figure 2.20).

The 2,5-*cis* relationship of the two nitro-groups means the 2-methyl group occupies a *pseudo*-axial position in the structure, relatively proximate to the group R1 (Figure 2.20). Consequently, there is a significant n.O.e. correlation between these two groups. This single cross-ring correlation allows the assignment of stereochemistry for both compounds (241) and (243): for (241) R1=benzyl, R2=methyl; for (243) R1=methyl, R2=benzyl.

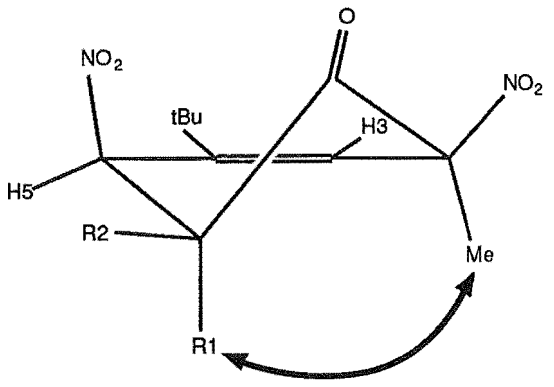
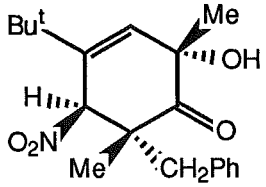


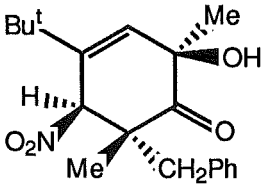
Figure 2.20 Cross-ring n.O.e. correlation for compounds (241) and (243).

With the structures of the four isomeric 2,5-dinitrocyclohex-3-enones (240), (241), (242) and (243) now established, it is of interest to compare the H3 chemical shifts for the pairs of C2-epimeric compounds. Earlier[73] it has been shown that for a pair of C2-epimeric 2,5-dinitrocyclohex-3-enones the resonance of H3 for the *trans*-dinitro compound occurs δ 0.10-0.20 ppm downfield of that for the corresponding *cis*-dinitro compound. For the C2-epimeric pairs, (240) and (241), and (242) and (243), the downfield chemical shift differences between *trans* and *cis* isomers are δ 0.09 ppm and δ 0.13 ppm respectively, paralleling the previously reported results.

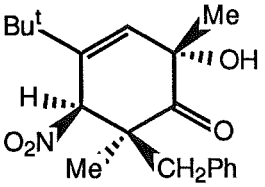
2.2.2.2 Three of the four possible stereoisomers (*d*-, *l* -pairs) of the 2-hydroxy-5-nitrocyclohex-3-enone gross structure were eluted from the silica gel plate in the elution order: compound (244) (2%), compound (245) (1%) and compound (246) (1%).



Compound (244)



Compound (245)



Compound (246)

The structural assignments to the hydroxy nitro ketones (244), (245) and (246) are based on (i) the single crystal X-ray structure determination for compound (246), (ii) the general similarity of the spectroscopic data for the three compounds, and (iii) results from selected n.O.e. difference experiments.

A perspective drawing of *t*-6-benzyl-4-*t*-butyl-*r*-2-hydroxy-2,6-dimethyl-*t*-5-nitrocyclohex-3-enone (246) is presented in Figure 2.21 (corresponding atomic coordinates are given in Section 3.3, Table 6).

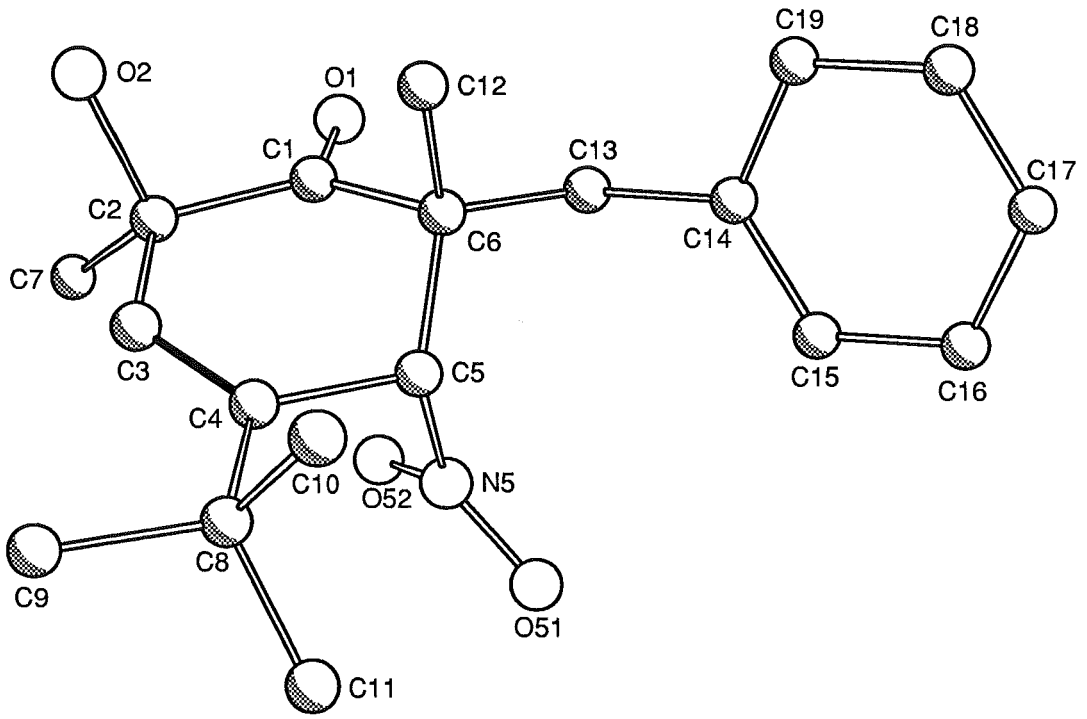


Figure 2.21 Perspective drawing of compound (246). Double bond shown in black.

In the solid state compound (246) exists as a skew boat [torsional angles: C1-C2-C3-C4 -8.3(9)°, C3-C4-C5-C6 31.8(7)°] with the 5-nitro group in the flagpole orientation. The plane of the 5-nitro group is close to being eclipsed with the C5-H5 bond [torsional angle, H5-C5-N5-O51 7.7(6)°], and the 5-nitro group is *anti* to the 6-methyl group [torsional angle: N5-C5-C6-C12 -175.9(5)°]. The conformation of the benzyl group is indicated by the torsional angles: C1-C6-C13-C14 172.1(5)°, C6-C13-C14-C15 94.6(7)°.

The n.m.r. spectroscopic data for compound (246) are in accord with the established structure. In particular, irradiation of the 2-methyl (C7) protons resulted only in a n.O.e. enhancement (8%) of the signal due to the H3 proton, and no effect was observed for the signals due to either the 6-methylene (C13) or the 6-methyl (C12) protons. On the basis of the results observed for the corresponding dinitro ketones (Section 2.2.2.1) these correlations are consistent with a *trans*-2-hydroxy-5-nitro relationship.

The stereochemical assignments for compounds (244) and (245) are based largely on the results of selected n.O.e. experiments. Irradiation of the 2-methyl protons in compound (244) resulted only in the enhancement (8%) of the signal due to the H3 proton, with no enhancement of either the 6-methylene signal or the 6-methyl signal. The absence of any correlation with the substituents at C6, suggests that compound (244) must have a *trans*-2-hydroxy-5-nitro relationship. Given the established structure for the hydroxy nitro ketone (246), by exclusion compound (244) must be its C6-epimer. In contrast, irradiation of the 2-methyl protons in compound (245) resulted in the enhancement not only of the signals due to the H3 proton (11%) but also of the AB quartet due to the C6-methylene protons (4%, downfield proton; 1%, upfield proton), although the signal due to the 6-methyl protons was not affected. By analogy with the arguments presented in Section 2.2.2.1 (in particular see Figure 2.20), compound (245) must have a *cis* relationship between the 2-methyl group and the C6-benzyl group. Compound (245) is thus defined as the C2-epimer of compound (244).

Interestingly, and in contrast to the significant effect of the C2-stereochemistry on the H3 chemical shifts for C2-epimeric 2,5-dinitro ketones (see ref. 73, and discussion above), the C2-stereochemistry for C2-epimeric 2-hydroxy-5-nitro ketones (244) and (245) has little effect on the H3 chemical shift [δ 6.22 ppm for the 2,5-*trans* compound (244), and δ 6.24 ppm for the 2,5-*cis* compound (245)].

2.2.3 Pathways in the reactions of 6-benzyl dienones (229) and (230) with nitrogen dioxide

2.2.3.1 The reactions of 6-benzyl-2-*t*-butyl-4,6-dimethylcyclohexa-2,4-dienone (230) with nitrogen dioxide may be rationalized in terms of the reaction pathways presented in Figure 2.22 below.

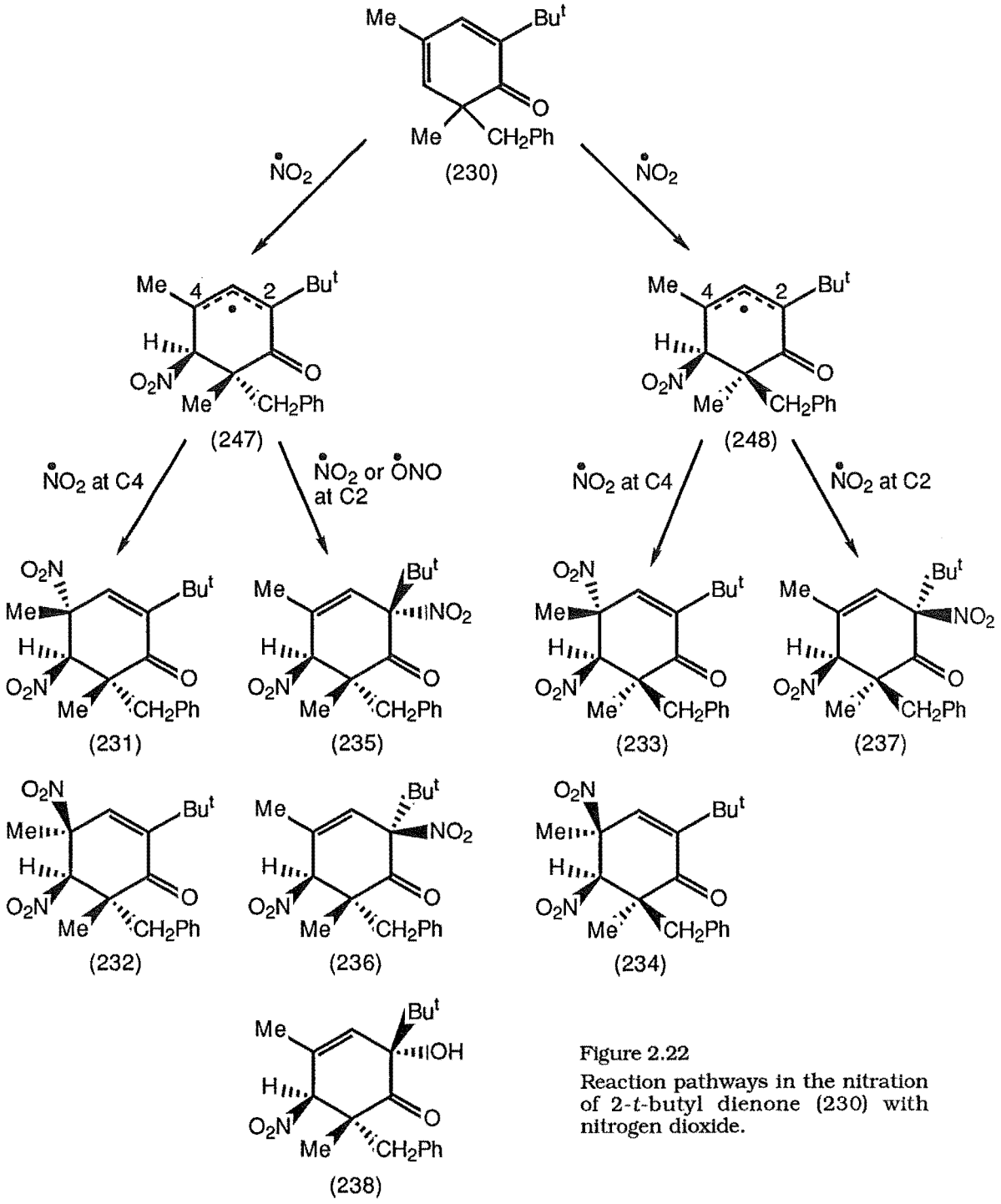


Figure 2.22
Reaction pathways in the nitration of 2-*t*-butyl dienone (230) with nitrogen dioxide.

Initial attack of nitrogen dioxide occurs at C5 to generate a delocalized radical, as was proposed for the reactions of the cyclohexa-2,4-dienones of 2,4,6-trialkyl phenols (see Section 2.1.1). In the case of the 2-*t*-butyl dienone (230) this initial attack may occur either *cis* (79%) or *trans* (17%) to the 6-methyl group, to generate the delocalized radicals (247) and (248) respectively. This selectivity for bond formation *cis* to the 6-methyl group is not surprising given the relative sizes of the two C6-substituents, the benzyl group hindering approach of a nitrogen dioxide molecule more than the much smaller methyl group.

Bond formation between the delocalized radical (247) and nitrogen dioxide may occur at either C2 or C4, although in terms of the steric arguments developed from the 2,4,6-trialkyl phenol studies[46,50,51] (see Section 2.1.1) bond formation to the less hindered C4-position should be preferred. In the event, bond formation occurs at both C2 and C4, although as predicted, products resulting from C4-bond formation predominate (*c.* 4:1) over those resulting from C2-bond formation. Attack of nitrogen dioxide at the less hindered C4-position of the delocalized radical (247) occurs exclusively with C-N bond formation to yield the two major products of reaction, compounds (231) and (232) (total yield 63%). In contrast, attack of nitrogen dioxide at the more hindered C2-position occurs with both C-N and C-O bond formation, although products resulting from C-N bond formation predominate (total yield 15%) over those resulting from C-O bond formation (total yield 1%). Attack at C2 with C-N bond formation generates the two C2-epimeric 2,5-dinitrocyclohex-3-enones (235) and (236), whereas attack with C-O bond formation gives a C2-nitrite ester (249), which on subsequent hydrolysis (see Figure 2.23) yields the 2-hydroxy-5-nitro compound (238).

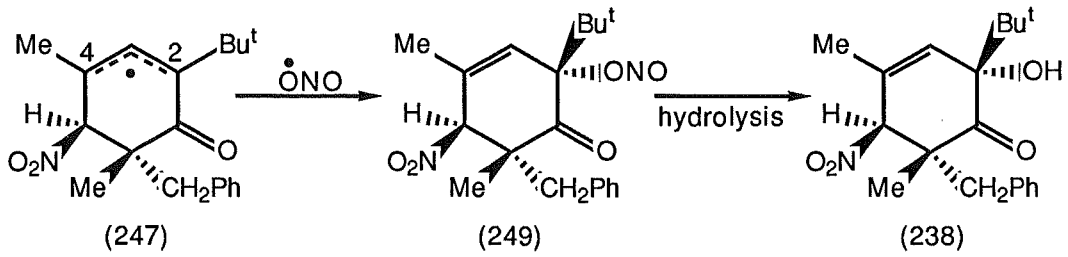


Figure 2.23 Formation of compound (238) *via* •ONO attack on the radical (247).

Further reaction of the minor isomeric delocalized radical (248) [arising from initial nitrogen dioxide attack on the dienone (230) *trans* to the 6-methyl group] may occur at either C2 or C4, although as was observed above

for the major isomeric delocalized radical (247), reaction at C4 is preferred (by an approximate ratio of *c.* 4:1). Bond formation at C4 yields the C4-epimeric dinitro ketones (233) and (234) (total yield 14%), while bond formation at C2 yields the *cis*-2,5-dinitro ketone (237) (3%). Attack at C2 with C-O bond formation undoubtedly occurs to some extent, but assuming a similar C-N: C-O bond formation ratio to that observed for the major isomer (247) (*c.* 15:1), the products thus formed would represent such a small percentage of the reaction mixture (*c.* 0.2%) that their isolation would be very unlikely.

A comparison of the reaction products from the dienone (230) with those isolated from the reaction of the parent phenol [2-*t*-butyl-4,6-dimethylphenol (216)], suggests that both the initial nitrogen dioxide attack at C5, and the subsequent radical coupling of the delocalized radical with nitrogen dioxide, are less stereoselective in the case of the dienone nitration. Although the two major products of reaction of the dienone (230) with nitrogen dioxide, compounds (231) and (232), are analogous to the two products observed on similar nitration of the phenol (216), the isolation of the additional compounds (233)-(238) from the dienone (230) nitration confirm the operation of the additional reaction pathways (illustrated in Figure 2.22 above) involving (i) initial nitrogen dioxide attack *trans* to the 6-methyl group, and (ii) recombination of the delocalized radicals (247) and (248) with nitrogen dioxide at C2.

2.2.3.2 The reactions of the 6-benzyl-4-*t*-butyl-2,6-dimethylcyclohexa-2,4-dienone (229) with nitrogen dioxide may be rationalized in terms of the reaction pathways illustrated in Figure 2.24 below. The initial attack of nitrogen dioxide on the 4-*t*-butyl dienone (229) is more stereoselective than that for the 2-*t*-butyl dienone (230) above, with products derived from further reaction of the delocalized radical (250), generated by initial nitrogen dioxide attack *cis* to the 6-methyl group, totalling some 92% of the material [*cf.* 79% for compound (230)].

At least in principle, reaction of nitrogen dioxide with the delocalized radical (250) could occur at either C2 or C4, although on the basis of the observations from the reaction of 4-*t*-butyl-2,6-dimethylphenol (206) with nitrogen dioxide (see Section 2.1.1.2), attack should occur predominantly, if not exclusively, at C2. In the event, the attack occurs exclusively at C2. The products generated from this radical combination reaction at C2 are of two types: those resulting from C2-N bond formation, and those resulting from

initial C2-O bond formation. The major reaction pathway involves C2-N bond formation, yielding the two 2,5-dinitro ketones (240) and (241) (total yield 89%); the minor reaction pathway involves initial C2-O bond formation and subsequent hydrolysis of the intermediate nitrite esters, in a manner analogous to that illustrated above for the 2-*t*-butyl dienone (see Figure 2.23), to give the hydroxy nitro ketones (244) and (245) (total yield 3%).

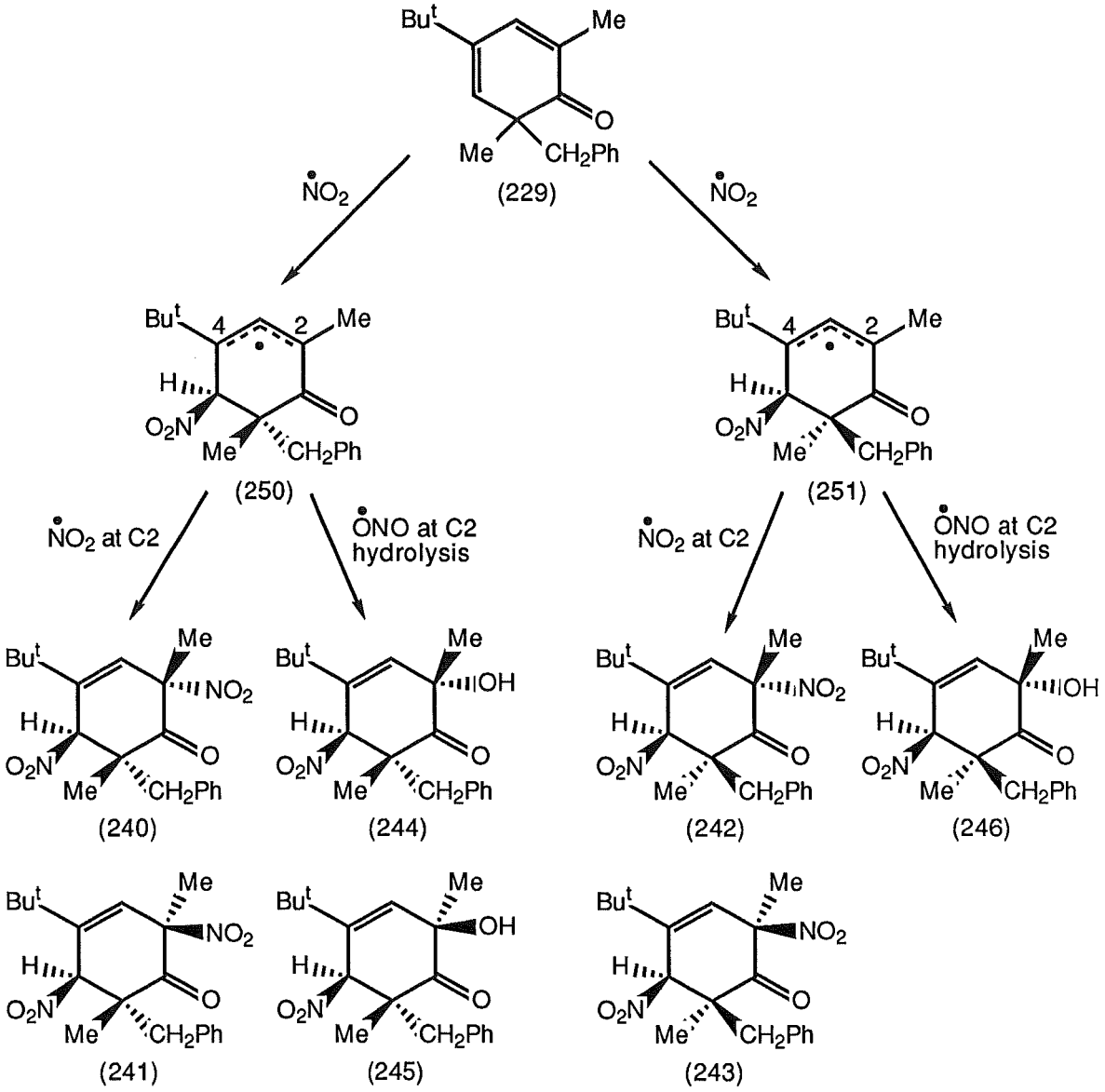


Figure 2.24 Reaction pathways in the nitration of the 4-*t*-butyl dienone (230) with nitrogen dioxide.

The reaction pathways available to the minor delocalized radical (251) are similar to those observed for the major isomeric delocalized radical (250). Attack of nitrogen dioxide at C2 with C-N bond formation yields the 2,5-dinitro ketones (242) and (243) (total yield 6%). Similarly attack at C2

with C-O bond formation, followed by hydrolysis, gives the hydroxy nitro ketone (246) (1%).

A comparison of the products from reaction of the dienone (229) with nitrogen dioxide, with those isolated from similar nitration of the parent phenol [4-*t*-butyl-2,6-dimethylphenol (206)], reveal some minor differences, although in general the reactions are very similar. In both cases the major products of reaction are the two C2-epimeric 2,5-dinitro ketones with a *cis* 5-nitro/6-methyl relationship. It is of interest to note that in the reaction of the dienone (229) the epimer with the *cis* 2,5-dinitro relationship (241) predominates over the corresponding *trans* 2,5-dinitro compound (240) (*c.* 1.8:1), whereas in the reaction of the parent phenol (206) with nitrogen dioxide it is the *trans* 2,5-dinitro compound which predominates over the corresponding *cis* isomer (*c.* 2:1). This effect may be a result of the large steric effect of the benzyl group which occupies a *pseudo*-axial position in both compounds (240) and (241) and may thus hinder to some extent approach of a nitrogen dioxide molecule from that side of the ring. An additional difference between the nitration reactions of the dienone (229) and its parent phenol (206), is the isolation of the three hydroxy nitro ketones (244), (245) and (246) from the reaction mixture of the dienone, no products of C2-O bond formation were isolated in the reaction of phenol (206) with nitrogen dioxide.

2.2.4 Rearrangement of *t*-6-benzyl-4-*t*-butyl-2,6-dimethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (241) in solution

During the isolation of the products of reaction of the 4-*t*-butyl dienone (229) with nitrogen dioxide, it became clear that the 2,5-dinitro ketone (241) was labile in solution. Indeed, when either a benzene or a chloroform solution of the dinitro ketone (241) was stored at 40°, it was converted, over a period of 45 days, into a mixture (*c.* 5:4:1:1:1:1) of the isomeric dinitro ketones (240), (242) and (243), and the three hydroxy nitro ketones (244), (245) and (246) respectively. Traces of the dienone (229) were also observed. In both of these reactions, the extent of rearrangement was monitored by withdrawing a sample from the solution periodically

and analyzing the percentage composition of that sample by ^1H n.m.r. spectroscopy. The isolation of the products listed above implied that isomerization could occur at C2 and at C5, although the presence of small quantities of dienone (229) in the mixture allows an alternative rationalization for the observation of C5-isomeric products - namely, that they arise from re-addition of nitrogen dioxide to the dienone (229). The experimental technique used in the above experiment was such that nitrogen dioxide could be lost from the reaction system, and so such a mechanism, involving reversion to the dienone (229), and subsequent re-addition of nitrogen dioxide is conceivable.

Reaction of the dinitro ketone (241) in deuteriochloroform in a sealed n.m.r. tube at 40° proceeded more slowly than the reaction monitored by periodic sampling and resulted only in isomerization at C2, confirming the required intermediacy of the dienone (229) in forming compounds (242), (243) and (246). The results of the rearrangement in deuteriochloroform are presented in graphic form in Figure 2.25.

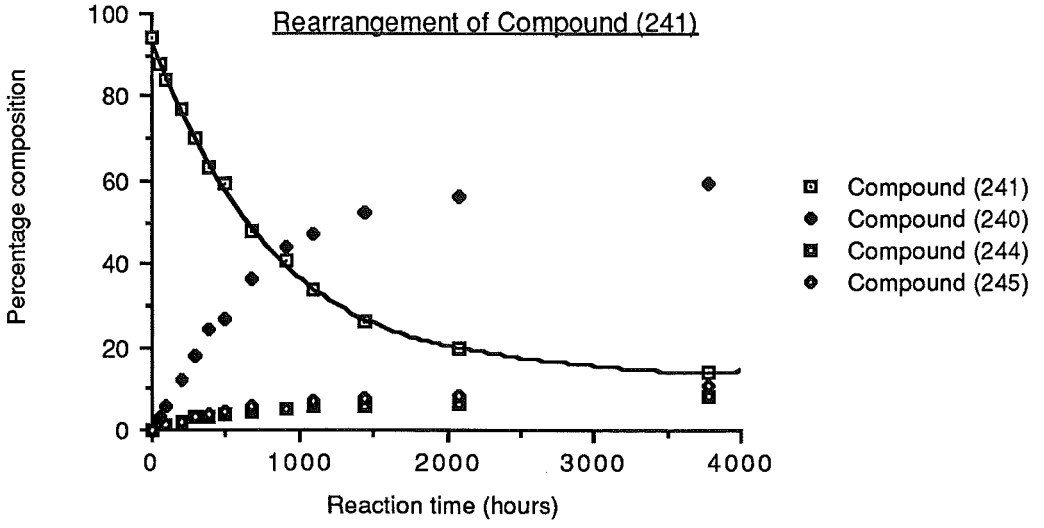


Figure 2.25 The rearrangement of compound (241) in deuteriochloroform at 40°.

The products of C2-epimerization, the dinitro ketone (240) and the two hydroxy nitro ketones (244) and (245), are envisaged as being formed by the reaction pathways shown in Figure 2.26 below. Homolysis of the C2-N bond would yield the radical pair (252) in a solvent cage. This radical pair (252) could recombine with C-N bond formation to either form dinitro ketone (241) or its C2-epimer (240), or alternatively, C2-O bond formation

could occur to give nitrite esters (253), which on hydrolysis by the traces of acid and water present in the deuteriochloroform, would yield the C2-epimeric 2-hydroxy-5-nitro ketones (244) and (245).

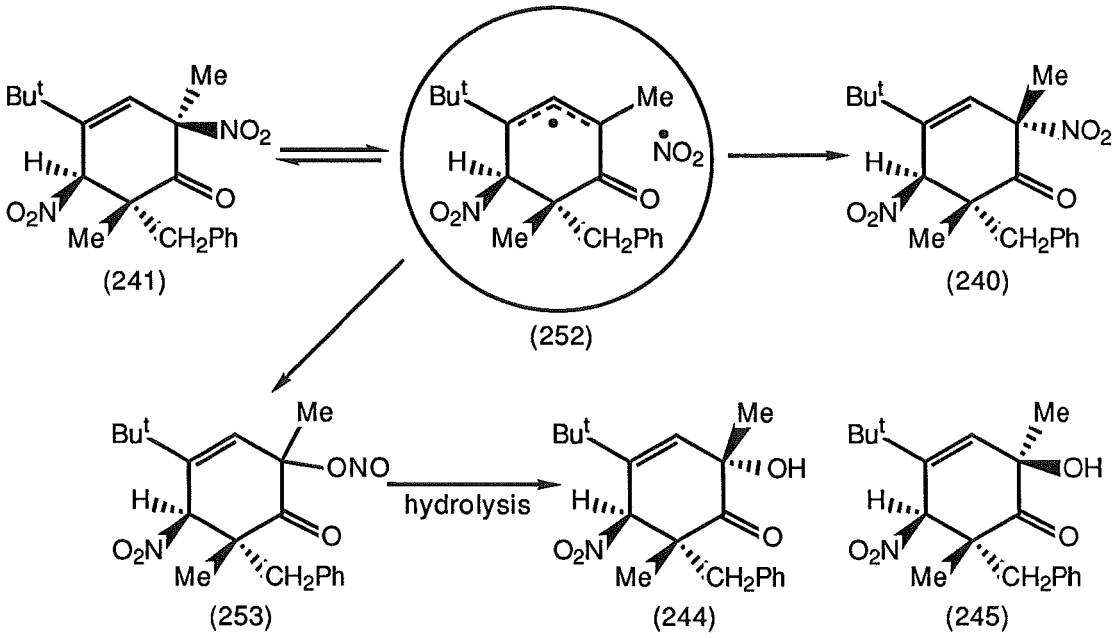


Figure 2.26 Mechanism for the rearrangement of compound (241) in solution.

In order to gain further insight into the mechanism of the initially observed rearrangement in benzene, where products of epimerization at both C2 and C5 were observed, several additional experiments were conducted.

(i) In separate experiments, the dinitro ketones (240) and (242) were stored in sealed n.m.r. tubes in deuteriochloroform at 40°, the samples being monitored periodically by ^{1}H n.m.r. spectroscopy. In both cases, and even after more than 30 days in solution, no products of isomerization were detectable by n.m.r. spectroscopy. These observations preclude the possibility of either of these compounds undergoing further rearrangement.

(ii) A small quantity of the dienone (229) was added to a sample of the dinitro ketone (241) in deuteriochloroform and this mixture then stored at 40° in a sealed n.m.r. tube. The extent of rearrangement was followed, as before, by periodic monitoring of the ^{1}H n.m.r. spectrum. In addition to the products of C2-epimerization, compounds (240), (244) and (245), products of epimerization at C5, namely compounds (242), (243) and (246) were also observed. Clearly, it is the presence of the dienone (229) which opens up a reaction pathway to C5-epimerization in the reactions of dinitro ketone (241). The nature of this reaction pathway is uncertain but two possibilities

would be: (i) reaction of free nitrogen dioxide with the dienone (229), and/or (ii) transfer of nitrogen dioxide from the delocalized radical (252) to a molecule of the dienone (229). In either case, the formation of the C5-epimeric delocalized radical could occur, and lead to the derived products (242), (243) and (246) by further reaction with nitrogen dioxide.

CHAPTER THREE

EXPERIMENTAL RELATING TO PART ONE

3.1 GENERAL EXPERIMENTAL METHODS

3.1.1 Materials and Instrumentation

Infrared spectra were recorded on Shimadzu IR-27G, or Pye-Unicam SP3-300 spectrophotometers, for liquid films, KBr disks and nujol mulls, with the 1603 cm^{-1} absorption band of polystyrene being used as a reference. Ultraviolet absorption spectra were recorded on a Varian DMS100 spectrophotometer. Mass spectra were recorded on a Kratos MS80RFA mass spectrometer.

Routine ^{1}H and ^{13}C n.m.r. spectra were obtained for deuteriochloroform solutions, with tetramethylsilane (TMS) as an internal reference, on a Varian XL300 Fourier transform spectrophotometer, operating at 300 MHz and 75 MHz for ^{1}H and ^{13}C nuclei respectively. All chemical shifts are expressed as parts per million (ppm) downfield from TMS, and are quoted as position (δ), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), relative integral and coupling constants (*J*, Hz). Difference nuclear Overhauser effect (n.O.e.) spectra were obtained in an arrayed experiment, with the decoupler offset 10000 Hz for the control experiment, using a procedure based on that of Kinns and Sanders.[74] They are reported as numerical percentages, indicating the percentage increase in the intensity of the observed hydrogen resonance. Two dimensional correlation spectra (COSY,[61] HETCOR,[62] and XCORFE[63]) were recorded in the usual manner, using standard software available on the Varian XL300 spectrophotometer.

Microanalyses were determined by Professor A. D. Campbell and associates, University of Otago.

Melting points were determined in open capillaries and are uncorrected.

Preparative scale chromatography was routinely carried out at both room temperature and at 0°, using a Chromatotron* (a preparative centrifugally accelerated, radial, thin layer chromatograph) equipped with rotors coated with Silica gel PF-254§ of various thicknesses (generally 2mm). For the low temperature separations all apparatus and solvents were stored at low temperature several hours before the actual separation.

High performance liquid chromatography (h.p.l.c.) was performed on a Shimadzu LC-4A liquid chromatograph using a Shimadzu SPD-2AS ultraviolet variable wavelength spectrophotometric detector, and a Hewlett Packard 3390A integrating recorder. Semi-preparative and analytical normal phase chromatography was carried out on an Alltech cyano-propyl column (25cm, 10mm I.D.) using either hexane/propan-2-ol or hexane/ dichloromethane solvent mixtures.

All solvents used were either of analytical grade (AR) or were purified and dried according to standard procedures. "Ether" refers to commercial diethyl ether distilled off sodium hydride, and "petroleum ether" refers to petroleum ether (50-70°) distilled off phosphorous pentoxide.

3.1.2 Synthesis of nitrogen dioxide

The nitrogen dioxide used, was prepared in a specially designed high-vacuum gas line (Figure 3.1), consisting of a 5-litre round flask with a cold-finger side arm, a mercury manometer, a gas inlet, and a set of liquid air cooled gas traps.

Pure, dry nitric oxide (NO, Matheson & Co.) (5-litre atmospheres) was added to the main flask (previously evacuated by high-vacuum pumping for 1 hour) and transferred by condensation at liquid air temperatures into the side arm. When the manometer indicated no residual pressure in the vacuum line (*i.e.* all nitric oxide condensed), pure dry oxygen (2.5 litre-atmospheres) was added rapidly to the main flask, and the cold trap was removed from the side arm, allowing the two gases to react. The main

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* Harrison Research Inc., model 7924.

§ Merck: E.M. Laboratories Inc., item 7749 (contains $CaSO_4.1/2H_2O$ type 60).

flask, sealed at tap A, was left overnight to allow the reaction to proceed to completion.

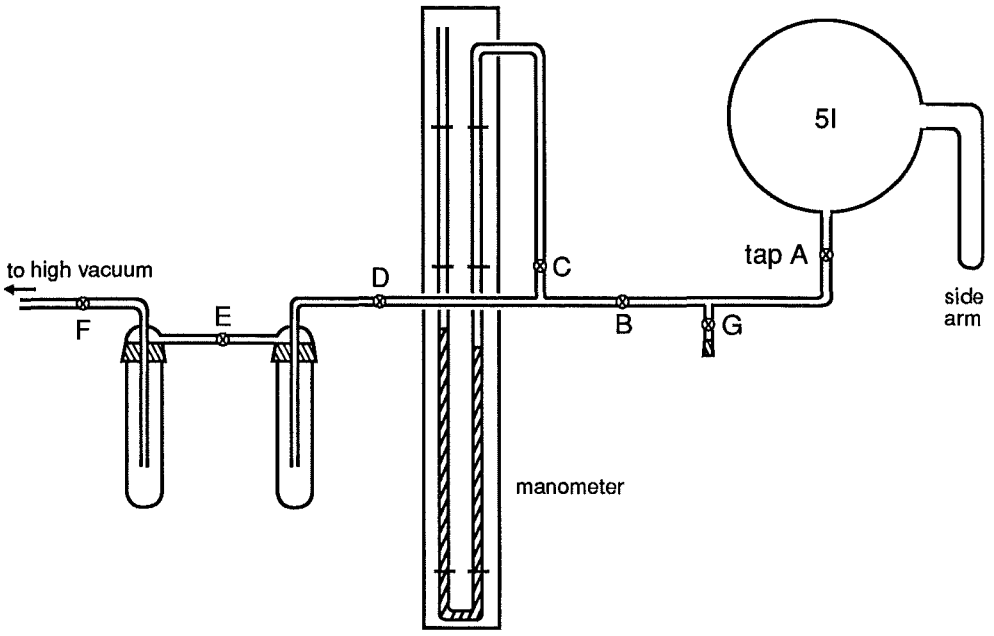

Figure 3.1 Apparatus for nitrogen dioxide synthesis.

The nitrogen dioxide thus formed was transferred into a specially designed 1-litre flask (Figure 3.2) where it was stored prior to use. During the transfer of nitrogen dioxide to the smaller flask, the crystalline material deposited in the cold-finger was colourless, indicating the presence of the dimeric dinitrogen tetroxide only. Other oxides of nitrogen, such as N_2O_3 and N_2O_5 are coloured and so their absence is implied. During the experimental work, the utmost care was taken to exclude atmospheric oxygen and water from the storage bulb.

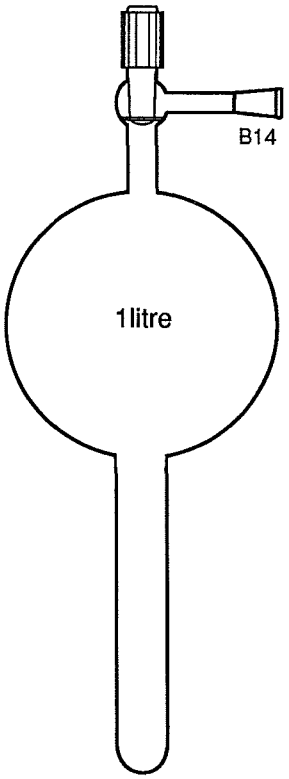

Figure 3.2 Nitrogen dioxide storage bulb.

3.2 EXPERIMENTAL RELATING TO CHAPTER TWO

3.2.1 2-*t*-butyl-4,6-dimethylphenol (215)

A solution of 2,4-dimethylphenol (40g), *t*-butyl alcohol (30g) and concentrated phosphoric acid (85% w/v, 130g) was placed in a 500ml 3-neck round-bottom flask, fitted with a reflux condenser and a mechanical stirrer. With the stirrer operating at a speed sufficient to mix the two layers, the solution was heated at 80-90° for 48 hours.[75] The solution was then cooled to room temperature and extracted with petroleum ether. The extracts were washed free of acid with water (blue litmus), dried ($MgSO_4$), and evaporated under reduced pressure to give a pale yellow liquid (50.7g, 87%) shown (^{1}H n.m.r.) to be essentially pure 2-*t*-butyl-4,6-dimethylphenol (215).

2-*t*-butyl-4,6-dimethylphenol (215)

^{1}H n.m.r. ($CDCl_3$) δ 1.41, s, 9H, *t*-butyl; 2.12, s, 3H, Me; 2.22, s, 3H, Me; *c*.4.5, bs, 1H, OH; 6.75, bs, 1H and 6.90, bs, 1H, H3 and H5.

3.2.2 6-benzyl-2-*t*-butyl-4,6-dimethylcyclohexa-2,4-dienone

To a solution of 2-*t*-butyl-4,6-dimethylphenol (8g) in toluene (110ml), was added sodium metal (1.04g), and the reaction to give the sodium salt was allowed to proceed to completion. After addition of benzyl chloride (16.2ml, 3 molar equivalents), the mixture was heated at 60-65° for 24 hours.[76] The solution was cooled to room temperature, and following the addition of petroleum ether (100ml), was washed with Claisen alkali* to remove any phenolic products. The yellow solution was then washed free of alkali with water, dried, and evaporated under reduced pressure to give a viscous yellow liquid (13.1g), shown (^{1}H n.m.r.) to contain approximately 15-20% dienone (230). The crude material was purified by chromatography, using a Chromatotron equipped with a silica gel plate and eluting with petroleum ether/ether (95:5), to give the pure dienone as a pale yellow solid.

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* Claisen alkali: 350g of KOH in 250ml of water per litre of solution in methanol.

***6-benzyl-2-t-butyl-4,6-dimethylcyclohexa-2,4-dienone* (230)**
m.p. 84-86° (Found: C, 84.85; H, 9.15. $C_{19}H_{24}O$ requires C, 85.02; H, 9.01%). ν_{max} (nujol) 1640 cm^{-1}, conjugated C=O. ^1H n.m.r. ($CDCl_3$) δ 1.16, s, 9H, *t*-butyl; 1.17, s, 3H, 6-Me; 1.85, d, 3H, $J_{4\text{-Me,H5}}$ 1.6 Hz, 4-Me; 2.66, d, 1H, $J_{geminal}$ 13.0 Hz, C$\underline{H}_2$Ph; 3.13, d, 1H, $J_{geminal}$ 13.0 Hz, C$\underline{H}_2$Ph; 5.88, dq, 1H, $J_{H5,4\text{-Me}}$ 1.6 Hz, $J_{H5,H3}$ 2.2 Hz, H5; 6.50, d, 1H, $J_{H3,H5}$ 2.2 Hz, H3; 7.02, m, 2H, *o*-Ph; 7.14, m, 3H, *m*- and *p*-Ph.

3.2.3 Reaction of 2-*t*-butyl dienone (230) with NO_2 in benzene

A solution of 6-benzyl-2-*t*-butyl-4,6-dimethylcyclohexa-2,4-dienone (300mg) in benzene (5ml) was de-oxygenated by a stream of nitrogen. The temperature was lowered to 0-5°, and nitrogen dioxide was bubbled through the solution for 30 seconds. The resulting brown solution was then stirred under an atmosphere of nitrogen dioxide for 2 hours at 0-5°. Following reaction, the excess nitrogen dioxide was removed in a stream of nitrogen, and the solvent removed under reduced pressure to give a yellow oil (410mg), shown by ^1H n.m.r. to be a mixture, consisting of two major, and a number of minor components. Separation of the crude product mixture by chromatography on a Chromatotron silica gel plate, and elution with petroleum ether/ether mixtures, allowed the isolation of six new compounds (listed below in order of elution).

***t*-6-benzyl-2-t-butyl-4,6-dimethyl-r-4,t-5-dinitrocyclohex-2-enone* (233)**
(6%)§ m.p. 137-138° (Found: C, 63.40; H, 6.79; N, 7.49. $C_{19}H_{24}N_2O_5$ requires C, 63.32; H, 6.71; N, 7.77%. Found: [M+H] *m/z* 361.1755. $C_{19}H_{25}N_2O_5$ requires 361.1763). ν_{max} (nujol) 1703, conjugated C=O; 1553, 1340 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 0.93, s, 3H, 6-Me; 1.32, s, 9H, *t*-butyl; 1.75, s, 3H, 4-Me; 2.55, d, 1H, $J_{geminal}$ 14.8 Hz, C$\underline{H}_2$Ph; 3.31, d, 1H, $J_{geminal}$ 14.8 Hz, C$\underline{H}_2$Ph; 5.72, d, 1H, $J_{H5,H3}$ 2.1 Hz, H5; 6.48, d, 1H, $J_{H3,H5}$ 2.1 Hz, H3; 7.13, m, 2H, *o*-Ph; 7.34, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 20.23, 27.22, methyls; 28.97, C($\underline{C}H_3)_3$; 35.66, $\underline{C}(CH_3)_3$; 38.68, $\underline{C}H_2$Ph; 48.15, C6; 83.64, C4; 93.76, C5; 127.30, 128.64, 128.90, 130.84, *o*-,*m*- and *p*-Ph and C3; 134.54, Ph1;* 148.47, C2; 194.85, C1.

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§ Percentage values refer to percentage composition of the original reaction product mixture.

* Ph1 refers to the non-protonated, substituted carbon in the phenyl ring.

In the absence of single crystal X-ray structure analysis data, the stereochemistry at the chiral centres was assigned on the basis of selected n.O.e. experiments (Figure 3.3), and by comparisons of the data thus obtained, with similar data for the structurally related compounds (231), (232) and (234).

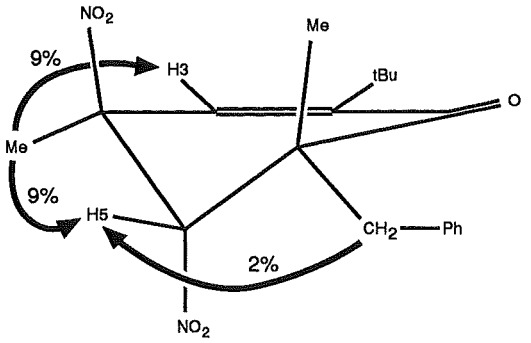

Figure 3.3 Observed n.O.e. enhancements for compound (233).

***c-6-benzyl-2-t-butyl-4,6-dimethyl-r-4,t-5-dinitrocyclohex-2-enone* (231)**

(23%) m.p. 103-105° (structure determination by single crystal X-ray analysis, see Section 3.3). ν_{max} (KBr disk) 1705, conjugated C=O; 1564 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.06, s, 3H, 6-Me; 1.34, s, 9H, *t*-butyl; 1.84, s, 3H, 4-Me; 2.65, d, 1H, $J_{geminal}$ 13.5 Hz, $C\underline{H}_2Ph$; 2.77, d, 1H, $J_{geminal}$ 13.5 Hz, $C\underline{H}_2Ph$; 5.84, d, 1H, $J_{H5,H3}$ 2.0 Hz, H5; 6.60, d, 1H, $J_{H3,H5}$ 2.0 Hz, H3; 6.91, m, 2H, *o*-Ph; 7.25, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 18.83, 26.63, methyls; 29.36, $C(\underline{C}H_3)_3$; 35.91, $\underline{C}(CH_3)_3$; 41.09, $\underline{C}H_2Ph$; 49.28, C6; 84.40, C4; 95.58, C5; 127.47, 128.22, 130.51, 130.76, *o*-,*m*- and *p*-Ph and C3; 133.60, Ph1; 148.08, C2; 194.23, C1.

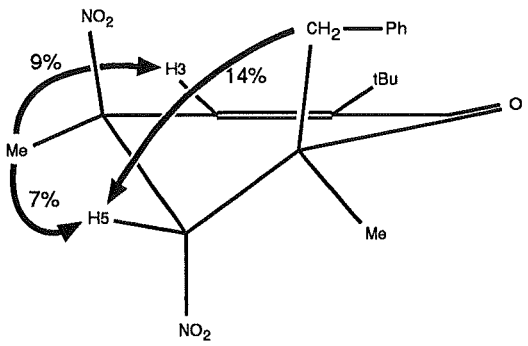

Figure 3.4 Observed n.O.e. enhancements for compound (231).

The stereochemistry at the chiral centres was initially assigned on the basis of selected n.O.e. experiments (Figure 3.4), and by comparisons of these data with similar data for the structurally related compounds (233), (232) and (234). The overall structure was confirmed by single crystal X-ray structure analysis.

***t-6-benzyl-2-t-butyl-4,6-dimethyl-r-4,c-5-dinitrocyclohex-2-enone* (232)**

(40%) m.p. 127-129° (structure determination by single crystal X-ray analysis, see Section 3.3). ν_{max} (nujol) 1703, conjugated C=O; 1574, 1562 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.22, s, 3H, 6-Me; 1.27, s, 9H, *t*-butyl; 1.69, s, 3H, 4-Me; 2.93, d, 1H, $J_{geminal}$ 13.8 Hz, $C\underline{H}_2Ph$; 3.30, d, 1H, $J_{geminal}$ 13.8 Hz, $C\underline{H}_2Ph$; 5.35, d, 1H, $J_{H5,H3}$ 1.2 Hz, H5; 6.87, d, 1H, $J_{H3,H5}$ 1.2 Hz, H3; 7.15, m, 2H, *o*-Ph; 7.29, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 22.27,

6-Me; 28.52, 2-Me; 29.13, C($\underline{C}H_3)_3$; 35.61, $\underline{C}(CH_3)_3$; 43.42, $\underline{C}H_2Ph$; 50.66, C6; 85.08, C4; 91.52, C5; 127.58, *p*-Ph; 128.63, *m*-Ph; 130.74, *o*-Ph; 133.25, C3; 134.82, Ph1; 148.55, C2; 195.64, C1.*

The stereochemistry at the chiral centres was initially assigned on the basis of selected n.O.e. experiments (Figure 3.5), and by comparisons of these data with similar data for the structurally related compounds (233), (231) and (234). The overall structure was confirmed by single crystal X-ray structure analysis.

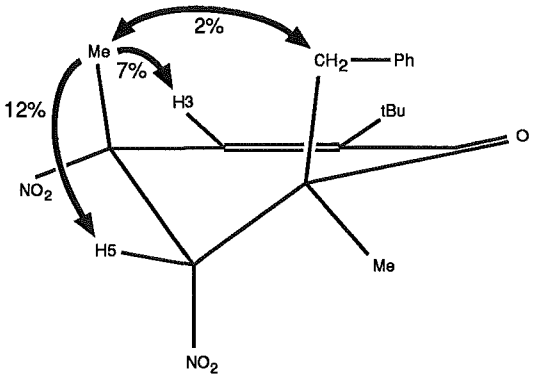

Figure 3.5 Observed n.O.e. enhancements for compound (232).

***t-6-benzyl-2-t-butyl-4,6-dimethyl-r-2,c-5-dinitrocyclohex-3-enone* (236)**

(8%) m.p. 110° (structure determination by single crystal X-ray analysis, see Section 3.3). ν_{max} (nujol) 1729, C=O; 1573, 1550 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.20, s, 9H, *t*-butyl; 1.24, s, 3H, 6-Me; 2.18, d, 3H, $J_{4\text{-Me,H3}}$ 1.5 Hz, 4-Me; 2.60, d, 1H, $J_{geminal}$ 13.5 Hz, $C\underline{H}_2Ph$; 3.01, d, 1H, $J_{geminal}$ 13.5 Hz, $C\underline{H}_2Ph$; 4.92, s, 1H, H5; 6.57, q, 1H, $J_{H3,4\text{-Me}}$ 1.5 Hz, H3; 7.11, m, 2H, *o*-Ph; 7.35, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 20.11, 22.75, methyls; 27.13, C($\underline{C}H_3)_3$; 41.42, $\underline{C}(CH_3)_3$; 42.60, $\underline{C}H_2Ph$; 51.91, C6; 92.45, C5; 93.86, C2; 127.59, 127.91, *p*-Ph and C3; 128.73, 130.71, *o*- and *m*-Ph; 133.73, 134.76, C4 and Ph1; 198.40, C1.

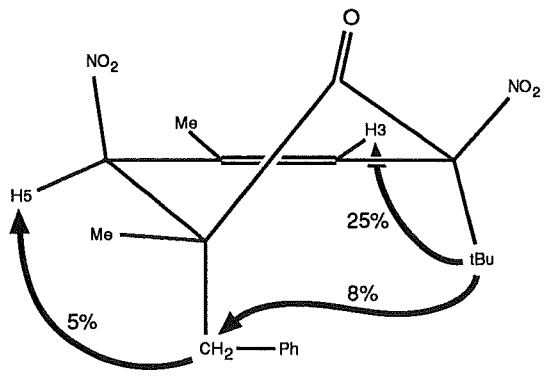

Figure 3.6 Observed n.O.e. enhancements for compound (236).

The stereochemistry at the chiral centres was initially assigned on the basis of selected n.O.e. experiments (Figure 3.6), and by comparisons of these data with similar data for the structurally related compounds (235), (238) and (237). The overall structure was confirmed by single crystal X-ray structure analysis.

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* HETCOR experiments were used to confirm carbon chemical shift assignments.

c-6-benzyl-2-t-butyl-r-2-hydroxy-4,6-dimethyl-t-5-nitrocyclohex-3-enone **(238)** (1%) m.p. 125.5-126° (Found: [M+H] *m/z* 332.1845. $C_{19}H_{26}NO_4$ requires 332.1862). ν_{max} (KBr disk) 3550, OH; 1724, C=O; 1558 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.16, s, 3H, 6-Me; 1.17, s, 9H, *t*-butyl; 2.04, d, 3H, $J_{4\text{-Me,H3}}$ 1.5 Hz, 4-Me; 2.52, s, 1H, OH; 2.72, d, 1H, $J_{geminal}$ 13.7 Hz, C$\underline{H}_2$Ph; 3.44, d, 1H, $J_{geminal}$ 13.7 Hz, C$\underline{H}_2$Ph; 4.90, s, 1H, H5; 6.22, q, 1H, $J_{H3,4\text{-Me}}$ 1.5 Hz, H3; 7.08, m, 2H, *o*-Ph; 7.32, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 17.68, 22.15, methyls; 26.30, C($\underline{C}H_3)_3$; 39.57, $\underline{C}(CH_3)_3$; 44.67, $\underline{C}H_2$Ph; 50.23, C6; 74.69, C2; 94.89, C5; 127.51, 133.45, *p*-Ph and C3; 128.50, 130.57, *o*- and *m*-Ph; 130.14, 134.91, C4 and Ph1; 209.12, C1.

In the absence of single crystal X-ray structure analysis data, the stereochemistry at the chiral centres was assigned on the basis of selected n.O.e. experiments (Figure 3.7), and by comparisons of the data thus obtained, with similar data for the structurally related compounds (235), (236) and (237).

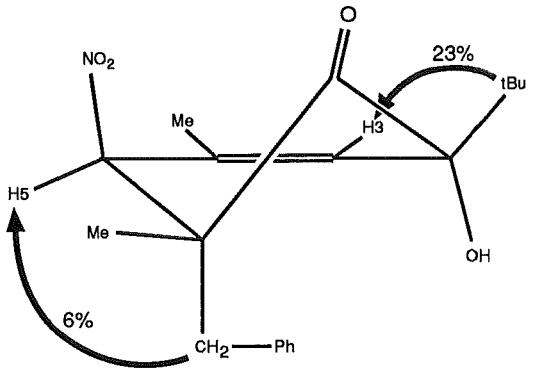

Figure 3.7 Observed n.O.e. enhancements for compound (238).

c-6-benzyl-2-t-butyl-4,6-dimethyl-r-2,c-5-dinitrocyclohex-3-enone **(237)** (3%) m.p. 105-108° (Found: [M+H] *m/z* 361.1767. $C_{19}H_{25}N_2O_5$ requires 361.1763). ν_{max} (KBr disk) 1732, C=O; 1551 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.10, d, 3H, $J_{6\text{-Me,methylene}}$ 0.8 Hz, 6-Me; 1.20, s, 9H, *t*-butyl; 2.10, d, 3H, $J_{4\text{-Me,H3}}$ 1.5 Hz, 4-Me; 2.79, dd, 1H, $J_{geminal}$ 14.5 Hz, $J_{methylene,6\text{-Me}}$ 0.8 Hz, C$\underline{H}_2$Ph; 3.38, d, 1H, $J_{geminal}$ 14.5 Hz, C$\underline{H}_2$Ph; 4.59, d, 1H, $J_{H5,H3}$ 0.6 Hz, H5; 6.44, qd, 1H, $J_{H3,4\text{-Me}}$ 1.5 Hz, $J_{H3,H5}$ 0.6 Hz, H3; 7.04, m, 2H, *o*-Ph; 7.32, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 21.32, 6-Me; 23.68, 2-Me; 27.13, C($\underline{C}H_3)_3$; 39.44, $\underline{C}H_2$Ph; 41.56, $\underline{C}(CH_3)_3$; 51.44, C6; 91.82, C5; 94.10, C2; 126.80, C3; 127.24, *p*-Ph; 128.54, *m*-Ph; 131.00, *o*-Ph; 134.53, 135.20, C4 and Ph1; 197.16, C1.§

In the absence of single crystal X-ray structure analysis data, the stereochemistry at the chiral centres was assigned on the basis of selected n.O.e. experiments (Figure 3.8), and by comparisons of the data thus

§ HETCOR experiments were used to confirm carbon chemical shift assignments.

obtained, with similar data for the structurally related compounds (235), (236) and (238).

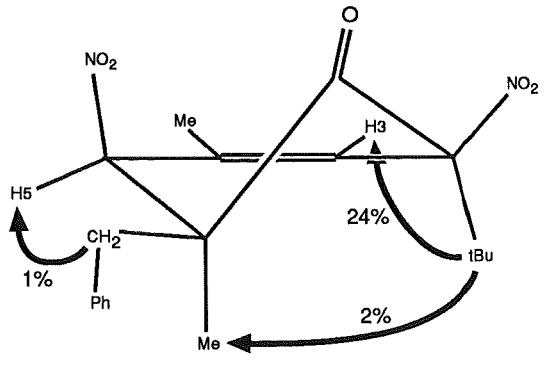

Figure 3.8 Observed n.O.e. enhancements for compound (237).

A further compound was isolated from the chromatographic separation, but was eluted over a very wide solvent range, in varying degrees of purity. This fact, coupled with the fact that its n.m.r. resonances are not observed in the ^{1}H n.m.r. spectrum of the crude product mixture, lead to its assignment as a decomposition product, formed during the chromatographic separation. It was purified by further chromatography on silica, and its structure assigned on the basis of its ^{1}H n.m.r. and i.r. spectroscopic data.

***6-benzyl-2-t-butyl-4,6-dimethyl-5-nitrocyclohexa-2,4-dienone* (239)**

(Found: [M+H] *m/z* 314.1755. $C_{19}H_{24}NO_3$ requires 314.1756). ν_{max} (liquid film) 1667, conjugated C=O; 1523, 1352 cm^{-1}, NO_2. ^{1}H n.m.r. ($CDCl_3$) δ 1.11, s, 9H, *t*-butyl; 1.46, s, 3H, 6-Me; 1.96, s, 3H, 4-Me; 3.23, d, 1H, $J_{geminal}$ 13.3 Hz, C$\underline{H}_2$Ph; 3.35, d, 1H, $J_{geminal}$ 13.3 Hz, C$\underline{H}_2$Ph; 6.37, s, 1H, H3; 7.04-7.20, m, 5H, Ph.

Although chromatographic separation using the Chromatotron allowed the isolation of the six reaction products, and one rearrangement product reported above, two further reaction products (accounting for approximately 15% of the total reaction product mixture) could not be isolated pure by chromatography on silica. Final purification of these two compounds (234) and (235) was achieved by h.p.l.c. on a cyano-propyl column. Impure samples of compound (235) were purified using 100% hexane as the eluting solvent, whereas compound (234) was purified using hexane/dichloromethane (80:20) solvent mixtures.

***c-6-benzyl-2-t-butyl-4,6-dimethyl-r-2,t-5-dinitrocyclohex-3-enone* (235)**

(7%) m.p. 107-109° (structure determination by single crystal X-ray analysis, see Section 3.3). ν_{max} (nujol) 1740, C=O; 1548 cm^{-1}, NO_2. ^{1}H n.m.r. ($CDCl_3$) δ 1.14, s, 3H, 6-Me; 1.25, s, 9H, *t*-butyl; 2.14, d, 3H, $J_{4\text{-Me,H3}}$ 1.5 Hz, 4-Me; 2.62, d, 1H, $J_{geminal}$ 13.3 Hz, C$\underline{H}_2$Ph; 2.73, d, 1H, $J_{geminal}$ 13.3 Hz, C$\underline{H}_2$Ph; 4.95, s, 1H, H5; 6.72, q, 1H, $J_{H3,4\text{-Me}}$ 1.5 Hz, H3; 6.99, m,

2H, *o*-Ph; 7.34, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 17.20, 22.18, methyls; 27.12, $C(\underline{C}H_3)_3$; 41.47, $\underline{C}(CH_3)_3$; 41.96, $\underline{C}H_2Ph$; 52.41, C6; 93.38, C2; 95.15, C5; 128.00, 128.96, *p*-Ph and C3; 128.81, 130.66, *o*- and *m*-Ph; 133.54, 133.60, C4 and Ph1; 196.62, C1.

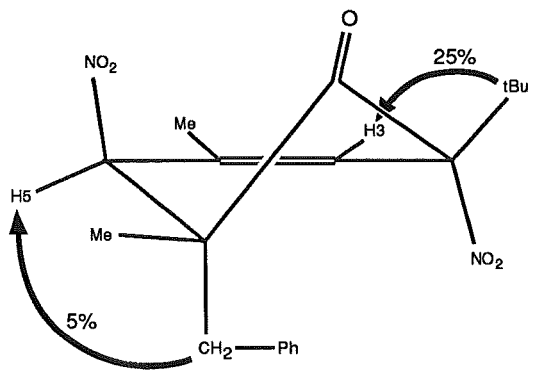

Figure 3.9 Observed n.O.e. enhancements for compound (235).

The stereochemistry at the chiral centres was initially assigned on the basis of selected n.O.e. experiments (Figure 3.9), and by comparisons of these data with similar data for the structurally related compounds (236), (238) and (237). The overall structure was confirmed by single crystal X-ray structure analysis.

***c-6-benzyl-2-t-butyl-4,6-dimethyl-r-4,c-5-dinitrocyclohex-2-enone* (234)**

(8%) m.p. 98-99° (Found: [M+H] *m/z* 361.1766. $C_{19}H_{25}N_2O_5$ requires 361.1763). ν_{max} (liquid film) 1700, conjugated C=O; 1576, 1561, 1343 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.16, s, 3H, 6-Me; 1.31, s, 9H, *t*-butyl; 1.90, s, 3H, 4-Me; 2.61, d, 1H, $J_{geminal}$ 14.8 Hz, $C\underline{H}_2Ph$; 3.28, d, 1H, $J_{geminal}$ 14.8 Hz, $C\underline{H}_2Ph$; 5.37, d, 1H, $J_{H5,H3}$ 1.9 Hz, H5; 6.71, d, 1H, $J_{H3,H5}$ 1.9 Hz, H3; 7.33, m, 5H, Ph. ^{13}C n.m.r. ($CDCl_3$) δ 23.20, 6-Me; 28.16, 4-Me; 28.95, $C(\underline{C}H_3)_3$; 35.67, $\underline{C}(CH_3)_3$; 38.44, $\underline{C}H_2Ph$; 50.28, C6; 87.55, C4; 95.67, C5; 127.23, *p*-Ph; 128.60, *m*-Ph; 130.01, C3; 131.14, *o*-Ph; 134.90, Ph1; 147.62, C2; 194.98, C1.

In the absence of single crystal X-ray structure analysis data, the stereochemistry at the chiral centres was assigned on the basis of selected n.O.e. experiments (Figure 3.10), and by comparisons of the data thus obtained, with similar data for the structurally related compounds (233), (231) and (232).

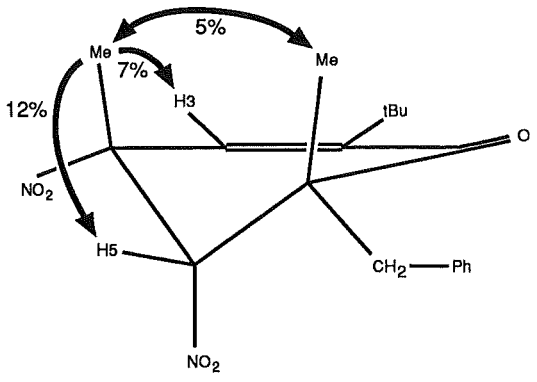

Figure 3.10 Observed n.O.e. enhancements for compound (234).

3.2.4 4-*t*-butyl-2,6-dimethylphenol (206)

A solution of 2,6-dimethylphenol (74g), *t*-butyl alcohol (55g, 1.25 molar equivalents) and concentrated phosphoric acid (85% w/v, 242g) was placed in a one litre 3-neck round-bottom flask, fitted with a reflux condenser and a mechanical stirrer. With the stirrer operating at a speed sufficient to mix the two layers, the solution was heated at 80-90° for 48 hours.[75] The solution was then cooled to room temperature and extracted with petroleum ether (3*100ml). The extracts were washed free of acid with water (blue litmus), dried ($MgSO_4$), and evaporated under reduced pressure to give a viscous pale orange/yellow liquid (108g, 99%) shown (^{1}H n.m.r.) to be essentially pure 4-*t*-butyl-2,6-dimethylphenol. The crude material was crystallized from petroleum ether, yielding three crops (44g, 41%) of pure phenol.

4-*t*-butyl-2,6-dimethylphenol (206)

m.p. 80-82° (lit.[77] 82.4°). ν_{max} (nujol) 3360, OH; 1606 cm^{-1}, aromatic. ^{1}H n.m.r. ($CDCl_3$, 60MHz) δ 1.27, s, 9H, *t*-butyl; 2.24, s, 6H, methyls; *c.* 4.5, s, 1H, OH; 7.01, s, 2H, H3 and H5 (lit.[78] δ 1.28, s, 9H; 2.23, s, 6H; *c.* 4.5, s, 1H; 6.98, s, 2H).

3.2.5 6-benzyl-4-*t*-butyl-2,6-dimethylcyclohexa-2,4-dienone

To a solution of 4-*t*-butyl-2,6-dimethylphenol (206) (5.7g) in toluene (76ml), was added sodium metal (740mg), and the reaction to give the sodium salt of the phenol was allowed to proceed to completion. After addition of benzyl chloride (11.5ml, 3 molar equivalents), the mixture was heated at 60-65° for 24 hours.[76] The solution was cooled to room temperature, and following the addition of petroleum ether (60ml), was washed with Claisen alkali to remove any phenolic products. The yellow solution was then washed free of alkali with water, dried, and evaporated under reduced pressure to give a viscous orange/red liquid (10.8g), shown (^{1}H n.m.r.) to contain approximately 30-35% dienone (229). The crude material was purified by chromatography, using a Chromatotron equipped with a silica gel plate and eluting with petroleum ether/ether (95:5), to give the pure dienone as a pale yellow oil.

***6-benzyl-4-t-butyl-2,6-dimethylcyclohexa-2,4-dienone* (229)**
(Found: C, 84.4; H, 8.9. $C_{19}H_{24}O$ requires C, 85.0; H, 9.0%. Found: *m/z* 268.1822. $C_{19}H_{24}O$ requires 268.1827). ν_{max} (liquid film) 2980, CH; 1663 cm^{-1}, conjugated C=O. ^1H n.m.r. ($CDCl_3$) δ 1.04, s, 9H, *t*-butyl; 1.24, s, 3H, 6-Me; 1.78, dd, 3H, $J_{2\text{-Me,H3}}$ 1.5 Hz, $J_{2\text{-Me,H5}}$ 0.5 Hz, 2-Me; 2.70, d, 1H, $J_{geminal}$ 12.3 Hz, C$\underline{H}_2$Ph; 3.12, d, 1H, $J_{geminal}$ 12.3 Hz, C$\underline{H}_2$Ph; 5.90, dq, 1H, $J_{H5,H3}$ 2.5 Hz, $J_{H5,2\text{-Me}}$ 0.5 Hz, H5; 6.71, dq, 1H, $J_{H3,H5}$ 2.5 Hz, $J_{H3,2\text{-Me}}$ 1.5 Hz, H3; 6.97, m, 2H, *o*-Ph; 7.13, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 15.74, 24.91, methyls; 28.93, C($\underline{C}H_3)_3$; 33.84, $\underline{C}(CH_3)_3$; 47.74, $\underline{C}H_2$Ph; 50.44, C6; 126.22, *p*-Ph; 127.27, 129.60, *o*- and *m*-Ph; 135.09, 139.25, C3 and C5; 132,50, 137.02, 139.83, C2, C4 and Ph1; 205.58, C1.

3.2.6 Reaction of 4-*t*-butyl dienone (229) with NO_2 in CH_2Cl_2

A solution of 6-benzyl-4-*t*-butyl-2,6-dimethylcyclohexa-2,4-dienone (229) (500mg) in dichloromethane (5ml) was de-oxygenated by a stream of nitrogen. The temperature was lowered to 0-5°, and nitrogen dioxide was bubbled through the solution for 30 seconds. The resulting brown solution was then stirred under an atmosphere of nitrogen dioxide for 2 hours at 0-5°. Following reaction, the excess nitrogen dioxide was removed in a stream of nitrogen, and the solvent removed under reduced pressure. The residue was an extremely viscous yellow liquid (680mg), shown by ^1H n.m.r. to be a mixture, consisting of two major, and several minor components. Separation of the crude product mixture by chromatography on a Chromatotron silica gel plate, and elution with petroleum ether/ether mixtures, gave (in order of elution) compounds (242), (240), (244), (241) and (243), (245) and (246).

***t-6-benzyl-4-t-butyl-2,6-dimethyl-r-2,t-5-dinitrocyclohex-3-enone* (242)**
(4%)§ m.p. 62-67° (Found: C, 63.45; H, 6.66; N, 7.84. $C_{19}H_{24}N_2O_5$ requires C, 63.32; H, 6.71; N, 7.77%). ν_{max} (nujol) 2980, CH; 1740, C=O; 1562, 1359, 1345 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.05, s, 3H, 6-Me; 1.14, s, 9H, *t*-butyl; 2.08, s, 3H, 2-Me; 2.54, d, 1H, $J_{geminal}$ 14.7 Hz, C$\underline{H}_2$Ph; 3.39, d, 1H, $J_{geminal}$ 14.7 Hz, C$\underline{H}_2$Ph; 5.32, d, 1H, $J_{H5,H3}$ 1.2 Hz, H5; 6.39, d, 1H, $J_{H3,H5}$ 1.2 Hz, H3; 7.23, m, 2H, *o*-Ph; 7.32, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$)

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§ Percentage values refer to percentage composition of the original reaction product mixture.

δ 20.26, 24.15, methyls; 28.63, C($\underline{C}H_3)_3$; 36.93, $\underline{C}(CH_3)_3$; 37.55, $\underline{C}H_2Ph$; 51.61, C6; 89.15, C2; 91.40, C5; 127.18, 127.87, 128.52, 131.01, *o*-, *m*- and *p*-Ph and C3; 134.55, 143.39, C4 and Ph1; 197.63, C1.

In the absence of a single crystal X-ray structure analysis, the stereochemistry at the chiral centres was assigned by comparisons of the ^1H n.m.r. chemical shifts, and the n.O.e. difference experiment data, with similar data for the related compounds (241), (240) and (243) (see Section 2.2.2).

***c-6-benzyl-4-t-butyl-2,6-dimethyl-r-2,t-5-dinitrocyclohex-3-enone* (240)** (32%) m.p. 132.5-135° (dec.) (structure determination by single crystal X-ray structure analysis, see Section 3.3. Found: C, 63.45; H, 6.99; N, 7.63. $C_{19}H_{24}N_2O_5$ requires C, 63.32; H, 6.71; N, 7.77%). ν_{max} (nujol) 1737, C=O; 1566, 1549 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.05, s, 3H, 6-Me; 1.27, s, 9H, *t*-butyl; 2.10, s, 3H, 2-Me; 2.70, d, 1H, $J_{geminal}$ 14.2 Hz, $C\underline{H}_2Ph$; 3.10, d, 1H, $J_{geminal}$ 14.2 Hz, $C\underline{H}_2Ph$; 5.38, d, 1H, $J_{H5,H3}$ 1.0 Hz, H5; 6.50, d, 1H, $J_{H3,H5}$ 1.0 Hz, H3; 6.91, m, 2H, *o*-Ph; 7.26, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 18.04, 24.84, methyls; 29.15, C($\underline{C}H_3)_3$; 36.80, $\underline{C}(CH_3)_3$; 40.92, $\underline{C}H_2Ph$; 51.46, C6; 89.22, C2; 93.65, C5; 127.69, 128.46, 128.87, 131.12, *o*-, *m*- and *p*-Ph and C3; 133.51, 142.34, C4 and Ph1; 196.92, C1.

***c-6-benzyl-4-t-butyl-r-2-hydroxy-2,6-dimethyl-t-5-nitrocyclohex-3-enone* (244)** (2%) m.p. 183-184° (dec.) (Found: C, 69.3; H, 8.1; N, 3.9. $C_{19}H_{25}NO_4$ requires C, 68.9; H, 7.6; N, 4.2%). ν_{max} (nujol) 3530, OH; 1727, C=O; 1568 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.02, s, 3H, 6-Me; 1.21, s, 9H, *t*-butyl; 1.70, s, 3H, 2-Me; 2.60, d, 1H, $J_{geminal}$ 13.6 Hz, $C\underline{H}_2Ph$; 3.26, d, 1H, $J_{geminal}$ 13.6 Hz, $C\underline{H}_2Ph$; 5.32, d, 1H, $J_{H5,H3}$ 1.1 Hz, H5; 6.22, d, 1H, $J_{H3,H5}$ 1.1 Hz, H3; 7.11, m, 2H, *o*-Ph; 7.25, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 17.10, 26.38, methyls; 29.03, C($\underline{C}H_3)_3$; 36.24, $\underline{C}(CH_3)_3$; 41.82, $\underline{C}H_2Ph$; 49.84, C6; 70.07, C2; 94.60, C5; 127.24, 128.06, 130.59, 133.62, *o*-, *m*- and *p*-Ph and C3; 134.52, 138.75, C4 and Ph1; 207.66, C1.

In the absence of a single crystal X-ray structure analysis, the stereochemistry at the chiral centres was assigned by comparing the ^1H n.m.r. chemical shifts, and n.O.e. difference experiment data for the compound, with similar data for the related compounds (245) and (246) (see Section 2.2.2).

***t-6-benzyl-4-t-butyl-2,6-dimethyl-r-2,c-5-dinitrocyclohex-3-enone* (241)**
(57%) m.p. 133.5-134° (Found: C, 63.17; H, 6.88; N, 7.50. $C_{19}H_{24}N_2O_5$ requires C, 63.32; H, 6.71; N, 7.77%). ν_{max} (nujol) 1734, C=O; 1566, 1522, 1327 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.10, s, 3H, 6-Me; 1.28, s, 9H, *t*-butyl; 2.07, s, 3H, 2-Me; 2.68, d, 1H, $J_{geminal}$ 14.0 Hz, C$\underline{H}_2$Ph; 2.82, d, 1H, $J_{geminal}$ 14.0 Hz, C$\underline{H}_2$Ph; 5.35, d, 1H, $J_{H5,H3}$ 1.0 Hz, H5; 6.41, d, 1H, $J_{H3,H5}$ 1.0 Hz, H3; 7.00, m, 2H, *o*-Ph; 7.32, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 18.41, 28.09, methyls; 29.04, C($\underline{C}H_3)_3$; 36.77, $\underline{C}(CH_3)_3$; 42.07, $\underline{C}H_2$Ph; 52.44, C6; 87.22, C2; 92.39, C5; 127.77, *p*-Ph; 127.82, C3; 128.44, *m*-Ph; 130.06, *o*-Ph; 133.17, 144.13, C4 and Ph1; 197.36, C1.*

In the absence of a single crystal X-ray structure analysis, the stereochemistry at the chiral centres was assigned solely on the basis of the n.m.r. spectroscopic data. Selected n.O.e. difference experiments (Figure 3.11) were used to determine the relative stereochemical relationships between the substituents at C2, and those at C6.

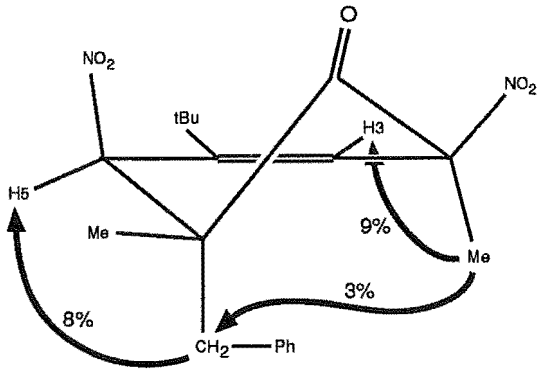

Figure 3.11 Observed n.O.e. enhancements for compound (241).

***c-6-benzyl-4-t-butyl-2,6-dimethyl-r-2,c-5-dinitrocyclohex-3-enone* (243)**
(2%) m.p. 128.5-129° (Found: C, 63.57; H, 6.75; N, 7.50. $C_{19}H_{24}N_2O_5$ requires C, 63.32; H, 6.71; N, 7.77%). ν_{max} (nujol) 1739, C=O; 1555 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.01, s, 3H, 6-Me; 1.16, s, 9H, *t*-butyl; 1.96, s, 3H, 2-Me; 2.57, d, 1H, $J_{geminal}$ 14.3 Hz, C$\underline{H}_2$Ph; 3.42, d, 1H, $J_{geminal}$ 14.3 Hz, C$\underline{H}_2$Ph; 5.25, d, 1H, $J_{H5,H3}$ 1.6 Hz, H5; 6.26, d, 1H, $J_{H3,H5}$ 1.6 Hz, H3; 7.19, m, 2H, *o*-Ph; 7.33, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 21.05, 28.50, methyls; 28.54, C($\underline{C}H_3)_3$; 36.81, $\underline{C}(CH_3)_3$; 37.90, $\underline{C}H_2$Ph; 52.48, C6; 87.52, C2; 89.45, C5; 126.87, 127.35, 128.65, 131.09, *o*-, *m*- and *p*-Ph and C3; 134.31, 144.27, C4 and Ph1; 198.02, C1.

In the absence of a single crystal X-ray structure analysis, the stereochemistry at the chiral centres was assigned solely on the basis of the n.m.r.

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* HETCOR experiments were used to confirm chemical shift assignments.

spectroscopic data. Selected n.O.e. difference experiments (Figure 3.12) were used to determine the relative stereochemical relationships between the substituents at C2, and those at C6.

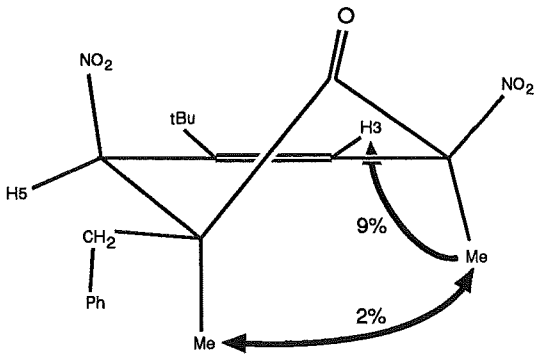

Figure 3.12 Observed n.O.e. enhancements for compound (243).

t-6-benzyl-4-t-butyl-r-2-hydroxy-2,6-dimethyl-c-5-nitrocyclohex-3-enone **(245)** (1%) m.p. 116° (dec.) (Found: C, 68.79; H, 7.77; N, 4.12. $C_{19}H_{25}NO_4$ requires C, 68.86; H, 7.60; N, 4.23%). ν_{max} (nujol) 3620, OH; 1727, C=O; 1553 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.00, s, 3H, 6-Me; 1.22, s, 9H, *t*-butyl; 1.64, s, 3H, 2-Me; 2.69, d, 1H, $J_{geminal}$ 14.1 Hz, $C\underline{H}_2Ph$; 2.99, d, 1H, $J_{geminal}$ 14.1 Hz, $C\underline{H}_2Ph$; 5.32, d, 1H, $J_{H5,H3}$ 1.3 Hz, H5; 6.24, d, 1H, $J_{H3,H5}$ 1.3 Hz, H3; 7.01, m, 2H, *o*-Ph; 7.30, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 18.01, 28.05, methyls; 29.14, $C(\underline{C}H_3)_3$; 36.21, $\underline{C}(CH_3)_3$; 41.35, $\underline{C}H_2Ph$; 52.56, C6; 70.67, C2; 95.19, C5; 127.55, 128.51, 129.93, 134.81, *o*-, *m*- and *p*-Ph and C3; 134.41, 139.99, C4 and Ph1; 210.23, C1.

In the absence of a single crystal X-ray structure analysis, the stereochemistry at the chiral centres was assigned solely on the basis of the n.m.r. spectroscopic data. Selected n.O.e. difference experiments (Figure 3.13) were used to determine the relative stereochemical relationships between the substituents at C2, and those at C6.

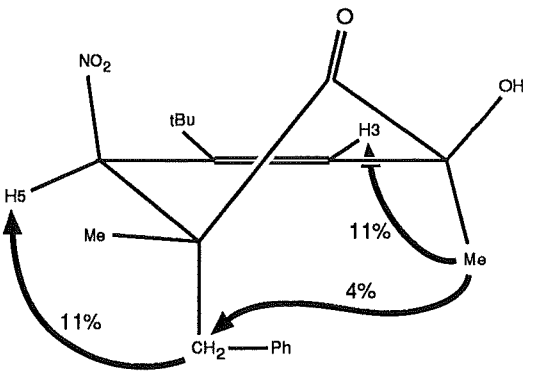

Figure 3.13 Observed n.O.e. enhancements for compound (245).

t-6-benzyl-4-t-butyl-r-2-hydroxy-2,6-dimethyl-t-5-nitrocyclohex-3-enone **(246)** (1%) m.p. 164-165° (structure determination by single crystal X-ray analysis, see Section 3.3). ν_{max} (nujol) 3550, OH; 1718, C=O; 1565 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.09, s, 3H, 6-Me; 1.09, s, 9H, *t*-butyl; 1.69, s, 3H, 2-Me; 2.46, d, 1H, $J_{geminal}$ 14.7 Hz, $C\underline{H}_2Ph$; 3.39, d, 1H, $J_{geminal}$ 14.7 Hz, $C\underline{H}_2Ph$; 5.22, d, 1H, $J_{H5,H3}$ 1.3 Hz, H5; 6.08, d, 1H, $J_{H3,H5}$ 1.3 Hz, H3; 7.23, m, 2H, *o*-Ph; 7.33, m, 3H, *m*- and *p*-Ph. ^{13}C n.m.r. ($CDCl_3$) δ 21.09, 25.64,

methyls; 28.82, C($\underline{C}H_3)_3$; 36.31, $\underline{C}(CH_3)_3$; 37.01, $\underline{C}H_2Ph$; 49.31, C6; 70.73, C2; 90.85, C5; 126.90, 128.36, 130.97, 132.82, *o*-, *m*- and *p*-Ph and C3; 135.22, 139.12, C4 and Ph1; C1 not observed.

3.2.7 Rearrangement of compound (241) in solution at 40°

In the course of the isolation and identification of compounds (243), (245) and (246), it was found that compound (241) in particular, undergoes rearrangement in solution.

(i) A solution of *t*-6-benzyl-4-*t*-butyl-2,6-dimethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (241) (50mg) in either benzene or chloroform (15ml) solution was stored at 40°, and the subsequent rearrangement followed by ^1H n.m.r. spectroscopy,* with a sample being drawn from the reaction solution at approximately 48 hour intervals. The results indicated a slow rearrangement of compound (241), giving after 45 days a mixture (*c.* 36:28:8:7:8:7:3) of compounds (240), (242), (243), (244), (245), (246) and (229) respectively.

(ii) A solution of *t*-6-benzyl-4-*t*-butyl-2,6-dimethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (241) (44mg) in $CDCl_3$ (0.6ml) was sealed in an n.m.r. tube, and the tube stored at 40°. The rearrangement was once again followed by ^1H n.m.r. spectroscopy, a spectrum being acquired at regular intervals. The rearrangement was somewhat slower than above, and after 45 days the mixture still contained approximately 50% of compound (241). Compounds (240), (244) and (245) (*c.* 34:6:5 respectively) were also detected in the mixture at this point.

(iii) A mixed sample (24mg), consisting of 85% compound (241) and 15% 6-benzyl-4-*t*-butyl-2,6-dimethylcyclohexa-2,4-dienone (229), was dissolved in $CDCl_3$ (0.6ml) and sealed in an n.m.r. tube, and the tube stored at 40°. The rearrangement was once again followed by ^1H n.m.r. spectroscopy, a spectrum being acquired at regular intervals. After 25 days the solution contained a mixture (*c.* 68:15:13:6:3:3:2:13) of compounds (241), (240), (242), (243), (244), (245), (246) and (229) respectively.

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* A relaxation delay (D1) of 20 seconds was used to ensure full relaxation of all protons.

3.2.8 Control reactions of compounds (240) and (242)

(i) Separate samples of compounds (240) and (242) in $CDCl_3$ were stored at 40°. Even after 25 days in solution, neither sample contained detectable quantities (by ^1H n.m.r.) of any rearrangement product.

3.3 SINGLE CRYSTAL X-RAY ANALYSES : PART ONE

The data sets used for the single crystal X-ray structure analyses of compounds (231), (232), (235), (236), (240) and (246) were collected on a Nicolet R3m four-circle diffractometer, using graphite monochromated Mo-K_α radiation (λ 0.71069 Å). Either Wyckoff or ω–scans were used to collect reflection intensities out to a Bragg angle θ, given below. The space group was in each case, determined on the basis of systematic absences of appropriate reflections. The cell parameters were determined by least squares refinement of at least 23 accurately centred reflections. Crystal stability was monitored by recording three check reflections every 100 reflections. The data sets were corrected for Lorentz and polarization effects but absorption corrections were not applied.

Crystal data for *c*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-4,*t*-5-dinitrocyclohex-2-enone (231) - $C_{19}H_{24}N_2O_5$, M 360.41, monoclinic, space group $P2_1/a$, a 10.244(3), b 11.838(3), c 15.436(4) Å, β 92.04(2) °, U 1870.8 Å^3, D_m 1.29 g cm^{-3}, D_c 1.28 g cm^{-3}, Z 4, μ(Mo K_α) 0.87 cm^{-1}. The crystal was colourless and of approximate dimensions 0.19 by 0.33 by 0.84 mm. Data was collected at a temperature of 183K using the Wyckoff scan technique. A total of 2263 reflections were collected, out to a maximum Bragg angle (θ) 22°. Of these reflections, 1990 were unique, and 1224 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0004; R-factor 0.0447; wR 0.0450.

Crystal data for *t*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-4,*c*-5-dinitrocyclohex-2-enone (232) - $C_{19}H_{24}N_2O_5$, M 360.41, monoclinic, space group $P2_1/c$, a 7.124(2), b 30.102(9), c 8.792(2) Å, β 93.50(2) °, U 1881.9 Å^3, D_m 1.27 g cm^{-3}, D_c 1.27 g cm^{-3}, Z 4, μ(Mo K_α) 0.86 cm^{-1}. The crystal was colourless and of approximate dimensions 0.27 by 0.45 by 0.68 mm. Data was

collected at a temperature of 173K using the ω-scan technique. A total of 2565 reflections were collected, out to a maximum Bragg angle (θ) 22°. Of these reflections, 2466 were unique, and 1566 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0005; R-factor 0.0503; wR 0.0519.

Crystal data for *c*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (235) - $C_{19}H_{24}N_2O_5$, M 360.41, monoclinic, space group $P2_1/c$, a 9.753(5), b 27.62(1), c 14.128(4) Å, β 101.21(3) °, U 3732.7 Å^3, D_m 1.24 g cm^{-3}, D_c 1.28 g cm^{-3}, Z 8, μ(Mo K_α) 0.87 cm^{-1}. The crystal was colourless and of approximate dimensions 0.37 by 0.54 by 0.80 mm. Data was collected at a temperature of 143K using the Wyckoff scan technique. A total of 5518 reflections were collected, out to a maximum Bragg angle (θ) 22°. Of these reflections, 4882 were unique, and 2901 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0012; R-factor 0.0507; wR 0.0530.

The structure consists of two, well separated, crystallographically independent molecules. Superposition of the two molecules , using the SHELXTL[79] program XFIT (Figure 2.15), revealed no gross differences of any chemical significance between the two molecules.

Crystal data for *t*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (236) - $C_{19}H_{24}N_2O_5$, M 360.41, monoclinic, space group $P2_1/c$, a 13.119(3), b 12.595(3), c 23.779(5) Å, β 104.07(2) °, U 3811.2 Å^3, D_m 1.23 g cm^{-3}, D_c 1.26 g cm^{-3}, Z 8, μ(Mo K_α) 0.85 cm^{-1}. The crystal was colourless and of approximate dimensions 0.35 by 0.55 by 0.68 mm. Data was collected at a temperature of 173K using the ω-scan technique. A total of 5671 reflections were collected, out to a maximum Bragg angle (θ) 22°. Of these reflections, 4956 were unique, and 2515 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0005; R-factor 0.0505; wR 0.0501.

The structure consists of two, well separated, crystallographically independent molecules. Superposition of the two molecules , using the SHELXTL[79] program XFIT (Figure 2.15), revealed no gross differences of any chemical significance between the two molecules.

Crystal data for *c*-6-benzyl-4-*t*-butyl-2,6-dimethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (240) - $C_{19}H_{24}N_2O_5$, M 360.41, orthorhombic, space group $P2_12_12_1$, a 16.417(5), b 16.012(6), c 7.215(2) Å, U 767.9 Å^3, D_m 1.26 g cm^{-3}, D_c 1.26 g cm^{-3}, Z 4, μ(Mo K_α) 0.86 cm^{-1}. The crystal was colourless and of

approximate dimensions 0.15 by 0.4 by 0.5 mm. Data was collected at a temperature of 183K using the ω-scan technique. A total of 2189 reflections were collected, out to a maximum Bragg angle (θ) 22°. Of these reflections, 2093 were unique, and 1661 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0021; R-factor 0.044; wR 0.049.

Crystal data for *t*-6-benzyl-4-*t*-butyl-*r*-2-hydroxy-2,6-dimethyl-*t*-5-nitrocyclohex-3-enone (246) - $C_{19}H_{25}NO_4$, M 331.41, monoclinic, space group $P2_1/c$, a 9.075(7), b 25.474(14), c 7.605(3) Å, β 94.26(5) °, U 1753 Å^3, D_m 1.25 g cm^{-3}, D_c 1.26 g cm^{-3}, Z 4, μ(Mo K_α) 0.82 cm^{-1}. The crystal was colourless and of approximate dimensions 0.12 by 0.19 by 0.64 mm. Data was collected at a temperature of 173K using the ω-scan technique. A total of 2642 reflections were collected, out to a maximum Bragg angle (θ) 22°. Of these reflections, 2270 were unique, and 874 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0016; R-factor 0.0556; wR 0.0576.

Intensity data were processed, and structure solution and refinement were carried out using a Data General Nova 4X computer, and the SHELXTL[79] system of programs. Diagrams were produced using the SHELXTL graphics program XP and a Tektronix 4113A colour graphics unit.

All the structures determined in this work were solved by direct methods and refined by blocked-cascade least squares techniques. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = [\sigma^2(F_o) + gF_o^2]^{-1}$. Anomalous dispersion corrections were from Cromer and Libermann.[80] All non-hydrogen atoms were assigned anisotropic thermal parameters, whereas hydrogen atoms were assigned thermal parameters equal to 1.2U of their carrier atoms. Methyl hydrogen atoms were included as rigid groups pivoting about their carbon atoms, with all other hydrogen atoms being included at idealized positions. Final Fourier syntheses showed no significant residual electron density and there were no abnormal discrepancies between observed and calculated structure factors.

Further, more comprehensive material regarding the structural information for the above structures (temperature factors, structure factor amplitudes, interatomic distances, bond angles and torsional angles) is deposited with the Editor-in-Chief, Editorial and Publications Service, CSIRO, 34 Albert Street, East Melbourne, Victoria 3002, Australia.

Table 1. Fractional coordinates for atoms in *c*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-4,*t*-5-dinitrocyclohex-2-enone (231)

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U^*
C(1)	7474(4)	306(3)	7385(2)	26(2)
C(2)	6146(4)	-96(3)	7638(2)	21(2)
C(3)	6052(4)	-736(3)	8353(2)	29(2)
C(4)	7138(5)	-1004(4)	8992(3)	29(2)
C(5)	8408(4)	-381(3)	8804(2)	28(2)
C(6)	8662(4)	-236(3)	7834(2)	24(2)
C(7)	4944(4)	288(4)	7102(3)	28(2)
C(8)	3698(4)	-265(4)	7413(3)	39(2)
C(9)	4805(5)	1563(4)	7225(3)	43(2)
C(10)	5067(5)	3(4)	6140(3)	42(2)
C(11)	6707(5)	-847(4)	9930(3)	44(2)
C(12)	9891(4)	477(4)	7728(3)	33(2)
C(13)	8853(4)	-1431(3)	7421(2)	28(2)
C(14)	9331(5)	-1437(3)	6502(2)	24(2)
C(15)	8466(4)	-1426(4)	5797(3)	34(2)
C(16)	8909(5)	-1465(4)	4964(3)	37(2)
C(17)	10216(6)	-1494(4)	4815(3)	39(2)
C(18)	11088(5)	-1501(4)	5512(3)	40(2)
C(19)	10657(5)	-1479(3)	6349(3)	31(2)
N(4)	7466(5)	-2281(3)	8954(2)	34(2)
N(5)	8350(4)	780(3)	9210(3)	38(2)
O(1)	7605(3)	1007(2)	6815(2)	35(1)
O(41)	6669(4)	-2910(3)	8570(2)	53(1)
O(42)	8449(3)	-2662(3)	9335(2)	46(1)
O(51)	7603(3)	1480(3)	8883(2)	43(1)
O(52)	9055(4)	975(3)	9841(2)	78(2)

* The equivalent isotropic temperature factor in this and the following Tables is defined as one-third of orthogonalized U tensor (Å2).

Table 2. **Fractional coordinates for atoms in *t*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-4,*c*-5-dinitrocyclohex-2-enone (232)**

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	1171(5)	3562(1)	9331(4)	33(1)
C(2)	1346(5)	3535(1)	7647(4)	29(1)
C(3)	1291(5)	3907(1)	6824(4)	33(1)
C(4)	1018(5)	4364(1)	7398(4)	31(1)
C(5)	414(4)	4385(1)	9046(4)	28(1)
C(6)	1327(5)	4020(5)	10105(4)	27(1)
C(7)	1558(5)	3077(1)	6924(4)	39(1)
C(8)	-143(6)	2784(1)	7216(5)	49(2)
C(9)	1692(7)	3108(1)	5201(4)	53(2)
C(10)	3371(6)	2856(1)	7587(5)	59(2)
C(11)	2740(5)	4664(1)	7158(4)	39(1)
C(12)	385(5)	4011(1)	11616(4)	39(1)
C(13)	3453(5)	4135(1)	10370(4)	33(1)
C(14)	4503(5)	3907(1)	11684(5)	44(2)
C(15)	5295(6)	3500(2)	11516(7)	69(2)
C(16)	6331(7)	3299(2)	12809(8)	91(3)
C(17)	6417(7)	3541(2)	14155(7)	89(3)
C(18)	5666(7)	3945(3)	14336(7)	92(3)
C(19)	4705(6)	4124(2)	13088(5)	66(2)
N(4)	-522(4)	4594(1)	6356(4)	37(1)
N(5)	-1693(4)	4334(1)	9067(4)	33(1)
O(1)	1017(4)	3236(1)	10121(3)	49(1)
O(41)	-1385(4)	4903(1)	6900(3)	56(1)
O(42)	-708(4)	4477(1)	5040(3)	63(1)
O(51)	-2455(3)	4028(1)	8359(3)	41(1)
O(52)	-2519(4)	4601(1)	9849(3)	47(1)

Table 3. Fractional coordinates for atoms in *c*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (235)

Molecule 1

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	3792(4)	3775(1)	-2928(3)	27(1)
C(2)	4816(4)	4193(1)	-2593(3)	27(1)
C(3)	4175(4)	4549(1)	-1986(3)	30(1)
C(4)	2924(4)	4516(1)	-1770(3)	31(1)
C(5)	1910(4)	4125(1)	-2185(3)	31(1)
C(6)	2222(4)	3881(1)	-3095(3)	28(1)
C(7)	6332(4)	4043(1)	-2082(3)	33(1)
C(8)	6224(4)	3733(2)	-1194(3)	37(2)
C(9)	7243(4)	4487(2)	-1718(3)	46(2)
C(10)	7108(4)	3761(2)	-2754(3)	39(2)
C(11)	2412(5)	4871(2)	-1106(3)	47(2)
C(12)	1402(4)	3416(1)	-3323(3)	34(1)
C(13)	1865(4)	4248(1)	-3942(3)	28(1)
C(14)	344(4)	4379(1)	-4220(3)	25(1)
C(15)	-194(4)	4785(1)	-3827(3)	27(1)
C(16)	-1573(4)	4921(1)	-4124(3)	31(1)
C(17)	-2424(4)	4665(1)	-4831(3)	29(1)
C(18)	-1922(4)	4265(1)	-5239(3)	31(1)
C(19)	-545(4)	4131(1)	-4935(3)	30(1)
N(2)	4952(3)	4456(1)	-3533(2)	28(1)
N(5)	1909(4)	3747(1)	-1406(2)	41(1)
O(1)	4206(3)	3373(1)	-3061(2)	36(1)
O(21)	4852(3)	4209(1)	-4262(2)	33(1)
O(22)	5186(3)	4892(1)	-3498(2)	37(1)
O(51)	2977(3)	3535(1)	-1109(2)	52(1)
O(52)	798(3)	3672(1)	-1136(2)	54(1)

Table 3. cont.

Molecule 2

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1')	1963(4)	3685(1)	2653(3)	28(1)
C(2')	847(4)	3321(1)	2165(3)	29(1)
C(3')	1398(4)	3010(1)	1445(3)	30(1)
C(4')	2681(4)	3024(4)	1269(3)	29(1)
C(5')	3770(4)	3357(1)	1797(3)	30(1)
C(6')	3498(4)	3533(1)	2775(3)	28(1)
C(7')	-620(4)	3550(1)	1736(3)	32(1)
C(8')	-420(4)	3940(2)	1005(3)	39(2)
C(9')	-1616(4)	3171(2)	1206(3)	46(2)
C(10')	-1327(4)	3777(2)	2518(3)	36(2)
C(11')	3142(4)	2693(1)	543(3)	38(2)
C(12')	4428(4)	3960(1)	3157(3)	38(2)
C(13')	3761(4)	3096(1)	3503(3)	30(1)
C(14')	5269(4)	2952(1)	3810(3)	28(1)
C(15')	5885(4)	2627(1)	3265(3)	36(2)
C(16')	7282(4)	2509(2)	3541(3)	43(2)
C(17')	8064(4)	2701(2)	4365(3)	45(2)
C(18')	7453(4)	3013(2)	4930(3)	43(2)
C(19')	6065(4)	3138(1)	4650(3)	36(2)
N(2')	623(3)	2981(1)	3000(2)	31(1)
N(5')	3885(4)	3797(1)	1166(2)	35(1)
O(1')	1649(3)	4075(1)	2918(2)	44(1)
O(21')	782(3)	3160(1)	3807(2)	39(1)
O(22')	309(3)	2562(1)	2816(2)	41(1)
O(51')	2831(3)	4044(1)	924(2)	45(1)
O(52')	5014(3)	3888(1)	959(2)	52(1)

Table 4. Fractional coordinates for atoms in *t*-6-benzyl-2-*t*-butyl-4,6-dimethyl-*r*-2,*c*-5-dinitrocyclohex-3-enone (236)

Molecule 1

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	3205(3)	7506(3)	1077(2)	24(2)
C(2)	3679(3)	6428(3)	1316(2)	23(2)
C(3)	4681(3)	6567(4)	1779(2)	26(2)
C(4)	4990(3)	7447(4)	2075(2)	27(2)
C(5)	4356(3)	8445(4)	1937(2)	26(2)
C(6)	3743(3)	8549(3)	1299(2)	23(2)
C(7)	3790(3)	5628(4)	817(2)	31(2)
C(8)	2716(4)	5209(4)	480(2)	53(2)
C(9)	4321(4)	6214(4)	399(2)	54(2)
C(10)	4469(4)	4667(4)	1059(2)	54(2)
C(11)	5928(3)	7496(4)	2572(2)	40(2)
C(12)	2925(4)	9427(4)	1226(2)	34(2)
C(13)	4546(3)	8791(4)	928(2)	28(2)
C(14)	4984(3)	9905(4)	984(2)	27(2)
C(15)	5849(4)	10191(4)	1427(2)	38(2)
C(16)	6211(4)	11216(4)	1477(2)	51(2)
C(17)	5744(4)	11988(4)	1089(2)	51(2)
C(18)	4903(4)	11705(4)	636(2)	48(2)
C(19)	4529(4)	10682(4)	587(2)	36(2)
N(2)	2887(3)	5894(3)	1623(2)	33(2)
N(5)	3600(3)	8464(3)	2331(2)	33(2)
O(1)	2423(2)	7528(2)	676(1)	40(1)
O(21)	3262(3)	5273(3)	2018(2)	51(1)
O(22)	1953(3)	6066(3)	1449(1)	49(1)
O(51)	2904(3)	7817(3)	2248(1)	43(1)
O(52)	3761(3)	9121(3)	2720(1)	56(2)

Table 4. cont.

Molecule 2

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1')	-1872(3)	6056(4)	1156(2)	25(2)
C(2')	-1319(3)	7129(3)	1344(2)	27(2)
C(3')	-307(3)	7003(4)	1804(2)	27(2)
C(4')	-6(3)	6141(4)	2112(2)	23(2)
C(5')	-655(3)	5142(4)	2010(2)	24(2)
C(6')	-1321(3)	5008(3)	1388(2)	22(2)
C(7')	-1186(4)	7834(4)	819(2)	36(2)
C(8')	-2212(5)	8054(6)	374(3)	95(3)
C(9')	-472(6)	7260(5)	513(3)	93(3)
C(10')	-693(7)	8887(5)	1021(3)	105(4)
C(11')	979(3)	6095(4)	2599(2)	37(2)
C(12')	-2157(4)	4149(4)	1342(2)	33(2)
C(13')	-551(3)	4726(3)	993(2)	25(2)
C(14')	-119(4)	3610(4)	1062(2)	28(2)
C(15')	834(4)	3379(4)	1444(2)	38(2)
C(16')	1218(4)	2341(4)	1497(2)	48(2)
C(17')	649(4)	1549(4)	1166(2)	47(2)
C(18')	-296(4)	1764(4)	783(2)	45(2)
C(19')	667(4)	2792(4)	731(2)	35(2)
N(2')	-2053(3)	7762(3)	1647(2)	39(1)
N(5')	-1391(3)	5173(3)	2418(2)	29(2)
O(1')	-2714(2)	6030(3)	814(1)	42(1)
O(21')	-1649(3)	8308(3)	2064(1)	61(2)
O(22')	-2995(3)	7719(3)	1454(2)	61(2)
O(51')	-2074(2)	5848(3)	2325(1)	37(1)
O(52')	-1235(3)	4539(3)	2816(1)	44(1)

Table 5. Fractional coordinates for atoms in *c*-6-benzyl-4-*t*-butyl-2,6-dimethyl-*r*-2,*t*-5-dinitrocyclohex-3-enone (240)

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	8217(2)	2350(2)	3910(5)	28(1)
C(2)	9164(2)	2405(2)	3532(5)	30(1)
C(3)	9563(2)	3184(2)	4237(5)	30(1)
C(4)	9176(2)	3859(2)	4852(5)	22(1)
C(5)	8242(2)	3875(2)	4784(5)	25(1)
C(6)	7828(2)	3024(2)	5129(5)	25(1)
C(7)	9354(3)	2225(2)	1499(6)	43(1)
C(8)	9603(2)	4616(2)	5753(5)	32(1)
C(9)	9260(2)	5446(2)	4990(6)	44(1)
C(10)	9444(2)	4570(2)	7853(6)	38(1)
C(11)	10538(2)	4598(2)	5407(7)	47(1)
C(12)	6898(2)	3078(2)	4754(5)	34(1)
C(13)	7997(2)	2813(2)	7242(5)	28(1)
C(14)	7503(2)	2101(2)	8041(5)	28(1)
C(15)	6823(2)	2274(2)	9137(6)	39(1)
C(16)	6363(2)	1629(2)	9926(6)	46(1)
C(17)	6578(2)	813(3)	9616(7)	49(1)
C(18)	7245(2)	632(2)	8540(7)	49(1)
C(19)	7716(2)	1274(2)	7762(6)	41(1)
N(2)	9528(2)	1676(2)	4696(5)	39(1)
N(5)	7988(2)	4186(2)	2857(4)	31(1)
O(1)	7841(2)	1765(1)	3300(4)	46(1)
O(21)	9781(2)	1826(2)	6261(5)	56(1)
O(22)	9523(2)	982(2)	4002(5)	69(1)
O(51)	8098(2)	3730(2)	1510(4)	43(1)
O(52)	7665(2)	4874(2)	2752(4)	55(1)

Table 6. **Fractional coordinates for atoms in *t*-6-benzyl-4-*t*-butyl-*r*-2-hydroxy-2,6-dimethyl-*t*-5-nitrocyclohex-3-enone (246)**

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	3928(6)	6819(3)	-1526(10)	44(3)
C(2)	4591(6)	6474(2)	-2892(11)	44(3)
C(3)	3978(6)	5933(2)	-2993(9)	38(3)
C(4)	3071(6)	5716(2)	-1898(10)	35(3)
C(5)	2598(6)	6042(2)	-394(9)	36(3)
C(6)	2470(6)	6630(2)	-773(8)	32(2)
C(7)	6271(6)	6466(2)	-2640(10)	55(3)
C(8)	2401(6)	5171(2)	-2171(9)	41(3)
C(9)	3045(7)	4878(2)	-3688(10)	60(3)
C(10)	703(6)	5239(3)	-2671(12)	71(3)
C(11)	2614(8)	4840(2)	-533(9)	57(3)
C(12)	1253(6)	6699(2)	-2312(8)	45(3)
C(13)	2122(6)	6969(2)	798(8)	40(3)
C(14)	613(6)	6876(2)	1517(10)	40(3)
C(15)	450(7)	6543(3)	2891(10)	50(3)
C(16)	-935(7)	6468(3)	3562(10)	60(3)
C(17)	-2148(7)	6728(3)	2810(11)	62(3)
C(18)	-1995(7)	7062(3)	1452(11)	61(3)
C(19)	-620(6)	7145(2)	762(9)	46(3)
N(5)	3691(6)	5963(2)	1183(9)	41(3)
O(1)	4458(4)	7243(2)	-1130(6)	51(2)
O(2)	4124(4)	6710(2)	-4587(7)	57(2)
O(51)	3328(5)	5718(2)	2463(7)	59(2)
O(52)	4918(5)	6162(2)	1104(7)	64(2)

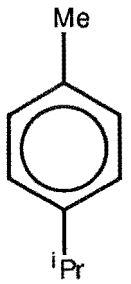
CHAPTER FOUR

THE NITRATION OF *PARA*-CYMENE

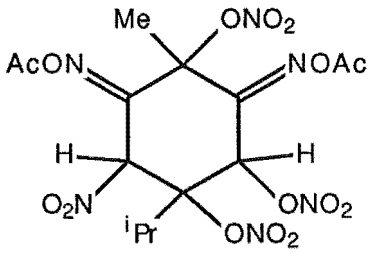
4.1 INTRODUCTION

4.1.1 Historical background

In 1933 N. Puranen reported the isolation of a white crystalline material (m.p. 127-129°), assigned structure (402), from the reaction of *p*-cymene (401) with nitrogen dioxide in acetic anhydride.[81] Despite the novel structure proposed by Puranen, no further studies of the nitration of *p*-cymene under these conditions have been reported. Addison *et al.*[24-28] have examined the nature of nitrogen dioxide/acetic anhydride as a reaction medium (see Section 1.2.4), but the reactions of this medium with aromatic compounds were not investigated.



Compound (401)



Compound (402)

In contrast, the nitration reactions of *p*-cymene under ionic conditions, where the active nitrating species is the nitronium ion, have been studied extensively.[82-85] In particular, the nitration of *p*-cymene in acetic anhydride with nitric acid has been thoroughly investigated by Fischer *et al.*[86] The characteristics of this reaction are summarized in Figure 4.1.

Although the two aromatic nitro compounds (403) and (404) arising from standard electrophilic aromatic substitution (EAS, see Section 1.1) are isolated as minor products of reaction (combined yield *c.* 30%), the two

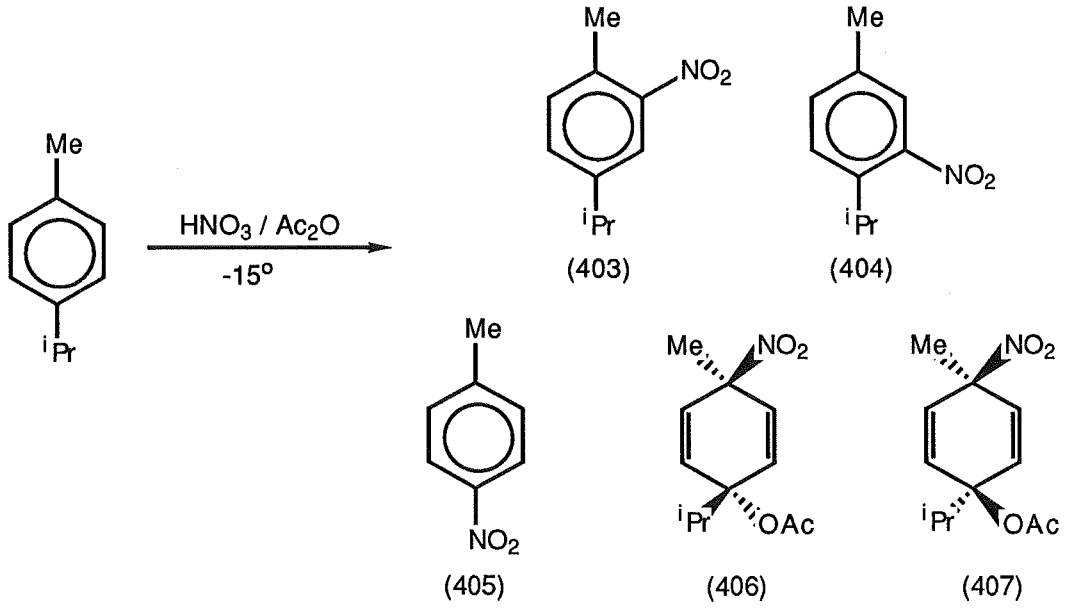


Figure 4.1 Reaction of *p*-cymene with nitric acid in acetic anhydride.

major products of reaction, compounds (406) and (407) (accounting for *c.* 60% of the total product mixture), are products of initial *ipso* attack at the methyl substituted carbon of the *p*-cymene molecule (Figure 4.2). Furthermore, compound (405) is also believed to be a product of initial *ipso* attack, arising from initial nitronium ion attack at the *iso*-propyl substituted carbon atom of the *p*-cymene molecule (Figure 4.2).

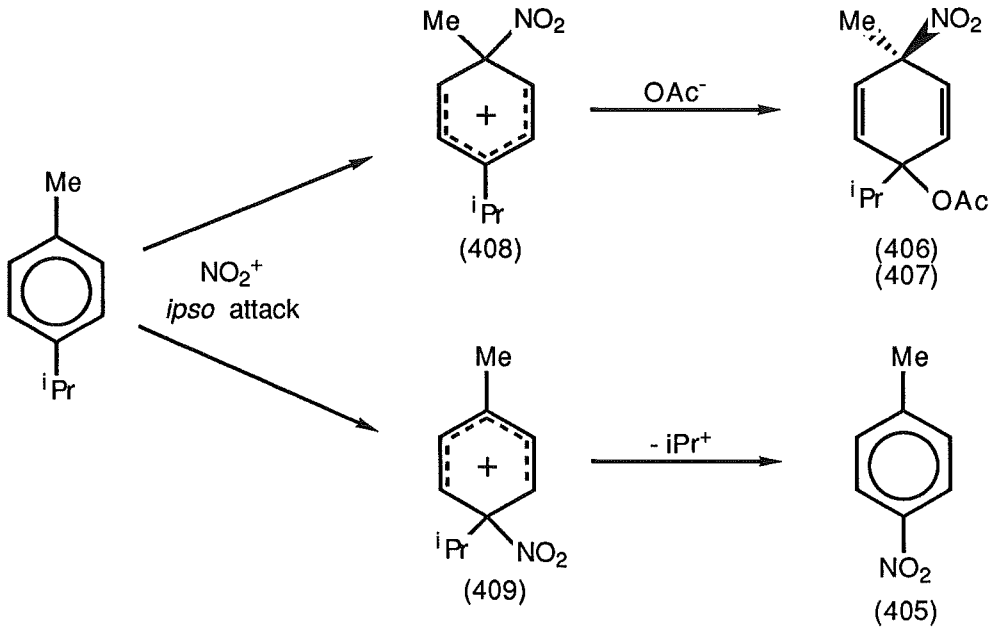


Figure 4.2 *Ipso* attack in the ionic nitration of *p*-cymene.

The respective fates of the two cationic Wheland intermediates (408) and (409) are quite different. For Wheland intermediate (408) subsequent reaction occurs *via* addition of an acetate anion *para* to the site of the initial *ipso* attack, yielding the two diastereoisomeric dienes (406) and (407). In contrast, the other Wheland intermediate (409) undergoes subsequent reaction by loss of the *iso*-propyl group, yielding *p*-nitrotoluene (405).

4.1.2 The present work

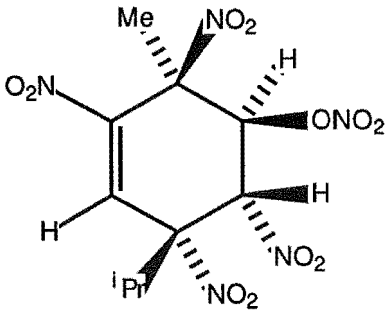
The novel structure postulated by Puranen[81] for the major product of reaction [compound (402), Section 4.1.1], coupled with our strong interest in *ipso*-nitration reactions, led us to reinvestigate the reaction between *p*-cymene and nitrogen dioxide in acetic anhydride. In the event, the reaction proceeds to give a very complex mixture of products, the isolation and characterization of a large percentage of these products being reported below. Some comment regarding mechanistic pathways to the formation of these reaction products is also presented.

4.2 DISCUSSION: THE NITRATION OF *PARA*-CYMENE IN ACETIC ANHYDRIDE

Reaction of *p*-cymene (401) with excess nitrogen dioxide in acetic anhydride for 24 hours, gave a crude product shown (^{1}H n.m.r.) to be a mixture (*c.* 24:8:3:3:16:4:4:4:1:1:5:4:5:1:4) of the four substituted aromatic compounds (403), (405), (414) and (415), and the eleven substituted cyclohexenes (410), (411), (412), (413), (416), (417), (418), (420), (419), (421) and (434) respectively. A wide variety of separatory techniques, including low temperature silica gel chromatography, h.p.l.c., and fractional crystallization were used to isolate and purify these compounds. The percentage yields quoted below, and in the Experimental Section, were estimated from the respective integrals in the ^{1}H n.m.r. spectrum of the crude product mixture, and do not reflect the amount of pure material isolated.

4.2.1 The isolation of compounds (410), (411), (412) and (413)

4.2.1.1 Crystallization of the residue, after removal of volatile material under reduced pressure, from ether/petroleum ether yielded the tetranitro nitrato cyclohexene (410)[87] (16%),* although the sample was somewhat contaminated with trace amounts of the closely related compounds (411), (412) and (413). Recrystallization from dichloromethane/hexane provided a pure crystalline sample of compound (410).



Compound (410)

Analysis of the spectroscopic data for the tetranitro nitrate (410) reveals a number of important features, which appear to be very characteristic of this type of structure. In the ^{1}H n.m.r. spectrum, two points are particularly worthy of note: (i) the coupling constant between H4 and H5 is large (11.6 Hz), requiring either a 0° coplanar, or alternatively a 180° *anti*-coplanar arrangement of the two C-H bonds, and (ii) the absence of any coupling to the hydrogen H2, implies the existence of the allylic nitro group at C1.

Nuclear Overhauser effect (n.O.e.) experiments also proved to be of great value in assigning the stereochemical relationships between the various proton-containing substituents. In particular, (i) a large enhancement of the H5 resonance was observed on irradiation of the 6-methyl resonance, indicating a *cis* relationship between these two substituents, and (ii) irradiation of the downfield methyl signal of the *iso*-propyl group, resulted in a large enhancement of the H4 signal, once again indicating a *cis* relationship between the two groups. These two facts, combined with the coupling constant information above, enable the assignment of the relative stereochemistry at all four chiral centres.

Although n.m.r. spectroscopy allows the assignment of the basic framework for the compound, the exact nature, and position of the nitro and nitrate substituents is more difficult to elucidate from spectroscopic information. Infrared spectroscopy confirms the existence of both nitro (1588, 1557 cm^{-1}) and nitrate (three strong absorptions at 1715, 1271, 811 cm^{-1})

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* Percentage values refer to percentage composition of the original reaction product mixture.

groups in the structure, but in order to be certain of the positions these substituents occupy in the structure, a single crystal X-ray structure analysis was undertaken. A perspective drawing of the structure is presented below (Figure 4.3) (corresponding atomic coordinates are given in Section 5.8, Table 7).

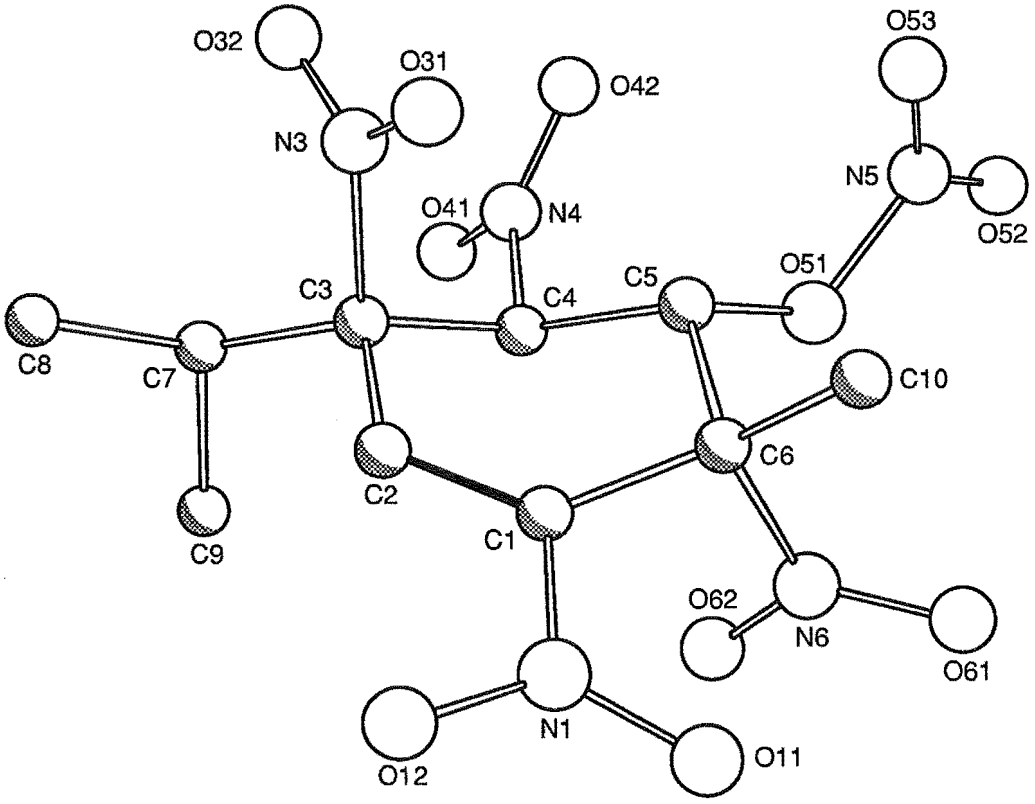
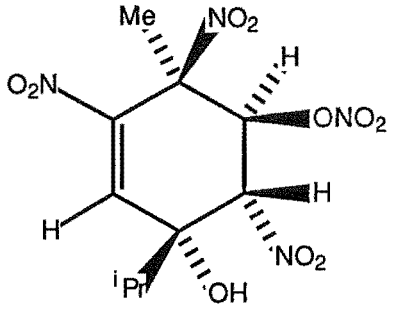


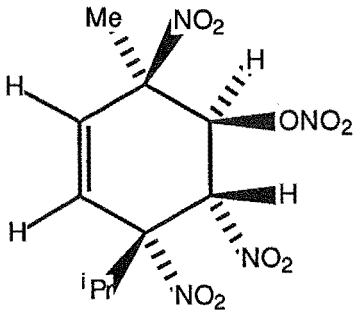
Figure 4.3 Perspective drawing of compound (410). Double bond shown in black.

In the solid state the alicyclic ring exists in a flattened skew-boat conformation [torsional angles: C1-C2-C3-C4 21.2(2)°; C2-C1-C6-C5 -4.1(2)°] in which the C6-substituents are close to being perfectly staggered with respect to the C1-nitro group. The relative orientation of the C5-nitrate and C6-methyl groups is indicated by the torsional angle C10-C6-C5-O51 84.9(2)°. Notwithstanding the above, H4 and H5 remain close to *anti*-coplanar [torsional angle: H4-C4-C5-H5 -175.5(1)°]. The close similarity between the conformation observed in the solid state (X-ray analysis), and the conformation in solution, implied by the spectroscopic information discussed above, suggests that the overall structure has a strongly preferred conformation, even in solution.

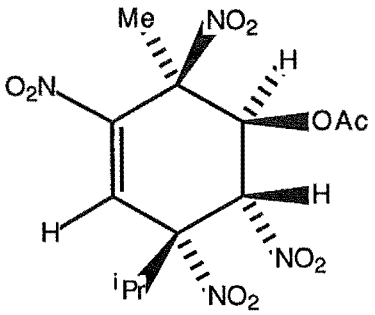
4.2.1.2 The residue from the above recrystallization of the tetranitro nitrate (410) was found to contain significant quantities of the three substituted cyclohexenes (411), (412) and (413). These three compounds were isolated by a combination of h.p.l.c. and fractional crystallization techniques.



Compound (411)



Compound (412)



Compound (413)

All three compounds display the large 11-12 Hz coupling constant between H4 and H5, in addition to the strong n.O.e. correlations between the 6-methyl group and H5, and one methyl group of the *iso*-propyl substituent and H4. This suggests that all three compounds have the same relative stereochemical relationships between the chiral centres C3, C4, C5 and C6, and identical to those observed for the tetranitro nitrate (410).

The ^{1}H n.m.r. spectrum for the hydroxy trinitro nitrate (411) (4%) showed a large upfield displacement (Δ 0.9 ppm) of the chemical shift for the *iso*-propyl hydrogen atom (H7), relative to the case of the tetranitro nitrate (410). This seems consistent with the replacement of the nitro group at C3 by some other substituent. Furthermore, the infrared spectrum showed a strong OH stretch absorption at 3350 cm^{-1}, also in accord with the assigned structure. The overall structure was confirmed by single crystal X-ray structure analysis (atomic coordinates are given in Section 5.8, Table 8), a perspective diagram for which is presented below (Figure 4.4).

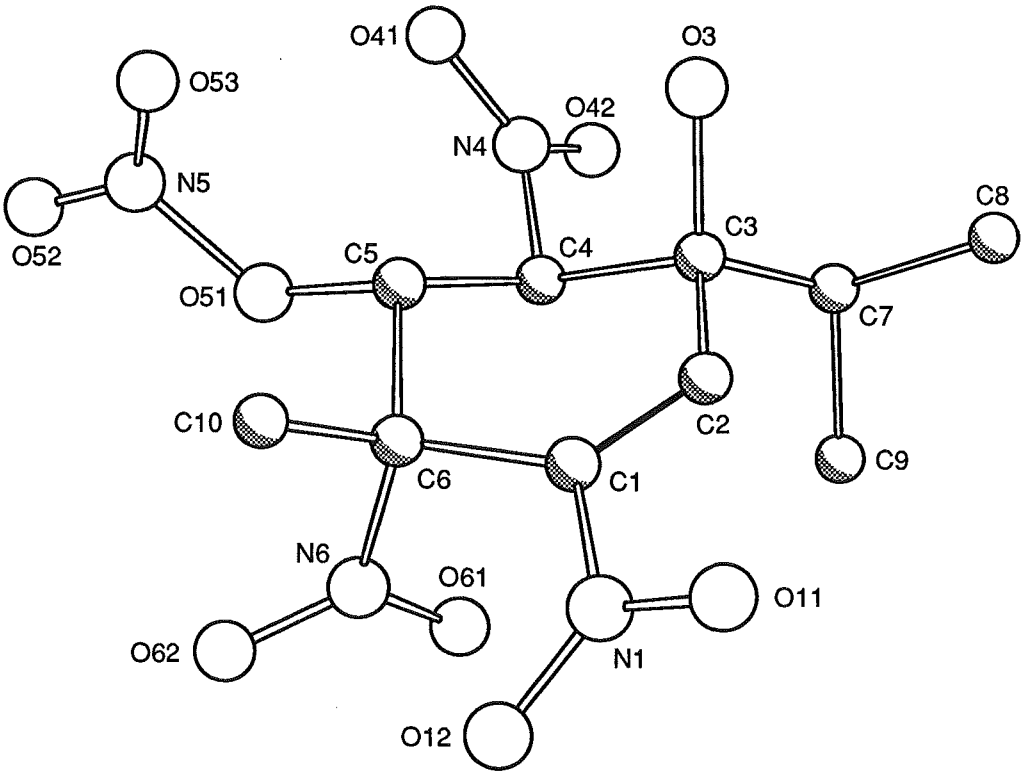


Figure 4.4 Perspective drawing of compound (411). Double bond shown in black.

In contrast to compound (410), the alicyclic ring of the hydroxy trinitro nitrate (411) exists in a flattened half-chair conformation in the solid state [torsional angles: C1-C2-C3-C4 -12.9(4)°; C2-C1-C6-C5 -8.9(4)°]. Despite the difference in conformation between the two compounds, H4 and H5 remain very close to *anti*-coplanar [torsional angle: H4-C4-C5-H5 174.5(0)°].

The trinitro nitrate (412) (4%), lacking the C1-nitro group of compounds (410) and (411), displays a somewhat different ^{1}H n.m.r. spectrum, particularly at higher (> 5 ppm) chemical shift values. The resonances for H4 and H5 retain their strong (11.7 Hz) coupling, indicative of their *anti*-coplanar relationship, but their chemical shifts are now coincidentally very similar, and so they appear as a tightly coupled AB quartet system, centred at δ 5.94 and 5.97 ppm respectively (Figure 4.5, below). The resonances for H1 and H2 also appear as an AB quartet system (*J* 10.1 Hz) centred at δ 6.18 and 6.24 ppm respectively (Figure 4.5, below).

As only very small quantities of the trinitro nitrate (412) were isolated, the simplest, and most conclusive method of characterization was by single crystal X-ray structure analysis. A perspective diagram of the structure is presented in Figure 4.6, below (corresponding atomic coordinates are given in Section 5.8, Table 9).

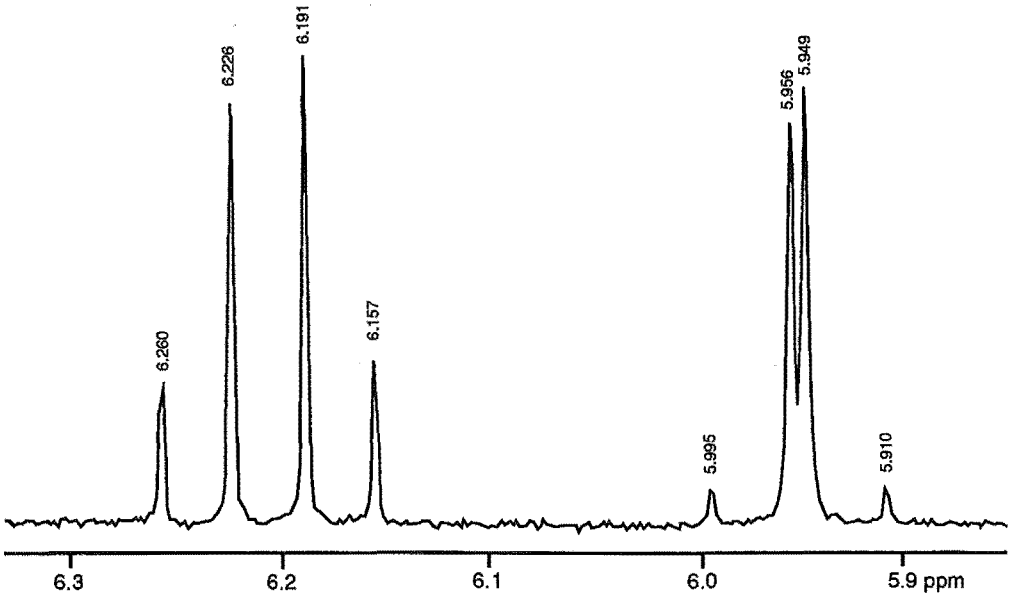


Figure 4.5 ^{1}H n.m.r. spectrum of the trinitro nitrate (412).

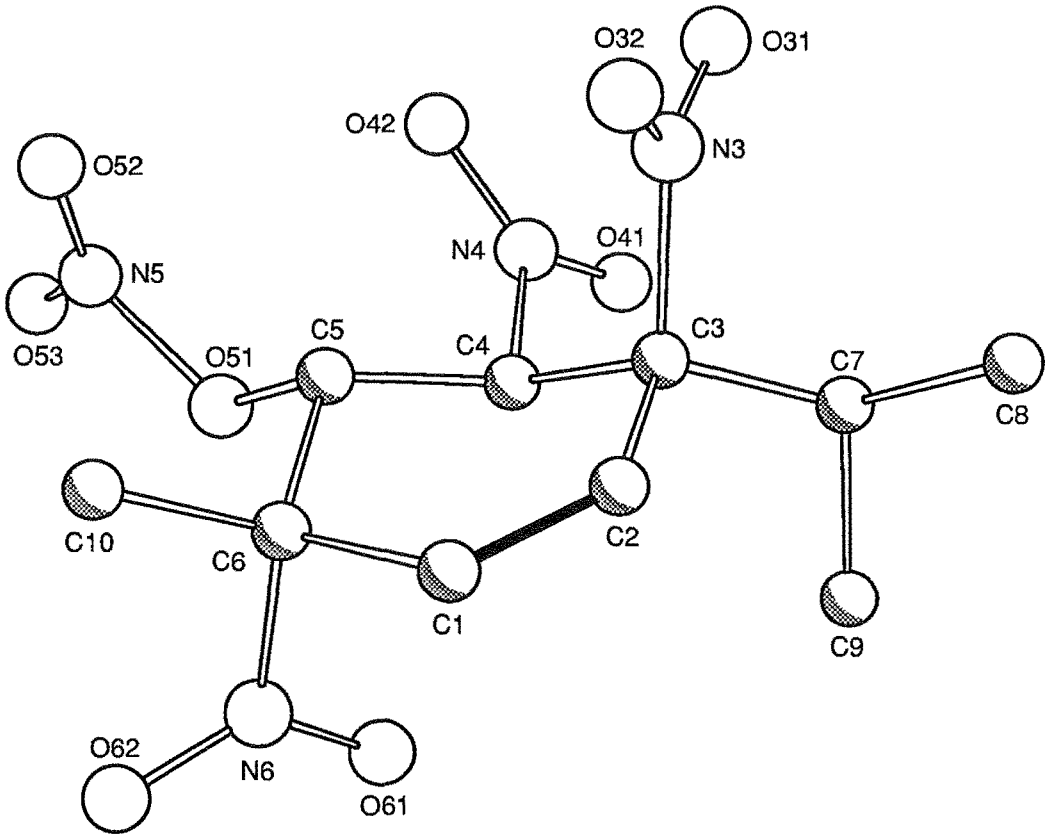


Figure 4.6 Perspective diagram of compound (412). Double bond shown in black.

In the solid state, the crystallographic asymmetric unit for compound (412) consists of two chemically equivalent, but crystallographically distinct molecules. Superposition of the two molecules (Figure 4.7) reveals no gross differences of any chemical significance between the two molecules.

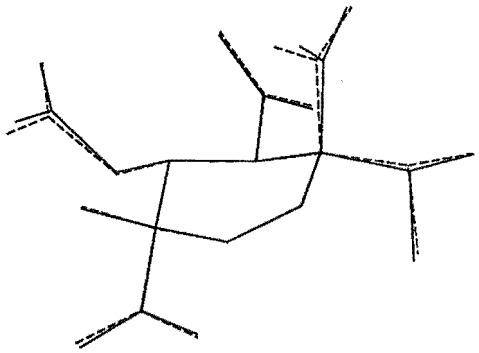


Figure 4.7 Superposition of two molecules of compound (412).

Both of the crystallographically independent molecules of compound (412) exist in flattened half chair conformations [torsional angles: molecule 1, C1-C2-C3-C4 -13.9(3)°, C2-C1-C6-C5 -7.1(3)°; molecule 2, C1'-C2'-C3'-C4' 15.7(0)°, C2'-C1'-C6'-C5' 6.6(0)°], and once again, H4 and H5 are close to *anti*-coplanar [torsional angles: molecule 1, H4-C4-C5-H5 176.6(0)°; molecule 2, H4'-C4'-C5'-H5' -178.5(0)°].

The tetranitro acetate (413) (4%) (see Figure 4.8) differs from the tetranitro nitrate (410) only in the nature of the C5 substituent, compound (413) having an acetate group, as opposed to the nitrate group in compound

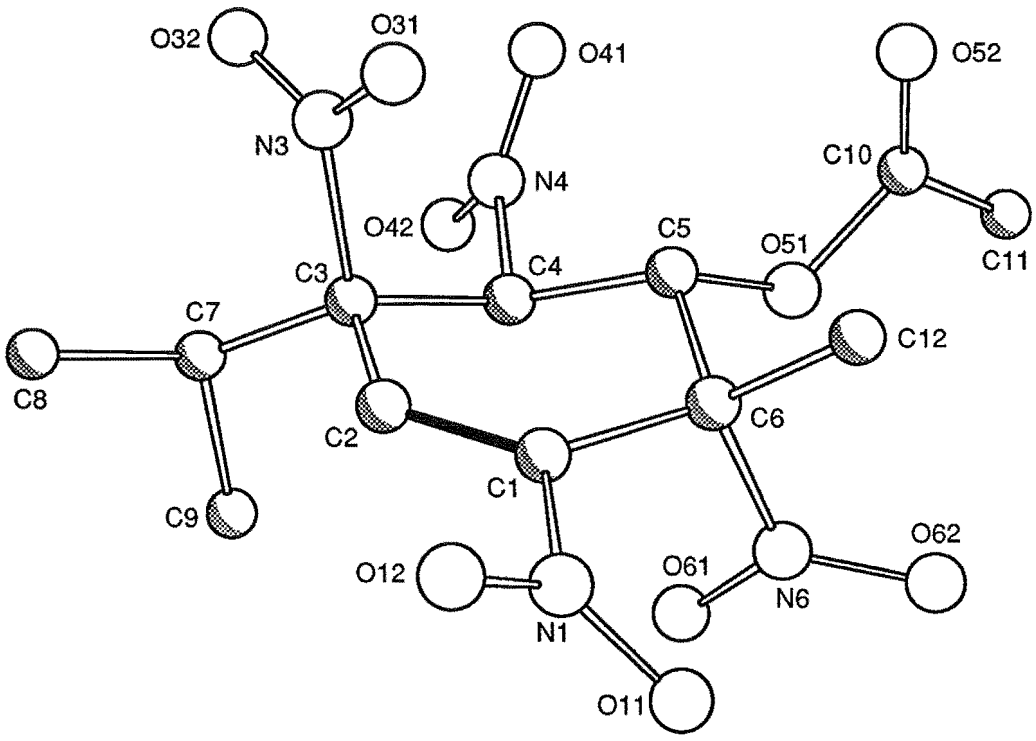
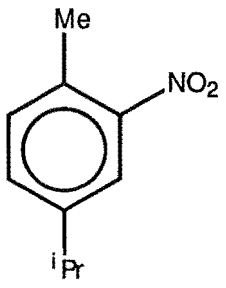


Figure 4.8 Perspective diagram of compound (413). Double bond shown in black.

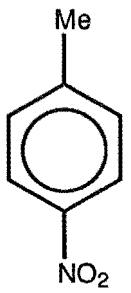
(410). The stereochemistry of this compound (413) is identical to that observed for the other three cyclohexenes (410), (411) and (412) referred to above. This is reflected in the close similarity of the n.m.r. chemical shift data, and in the magnitude of the n.O.e. correlations observed. Single crystal X-ray structure analysis of the tetranitro acetate (413) reveals that in the solid state the ring conformation is a flattened half chair, with the H4 and H5 groups still retaining their *anti*-coplanar relationship [torsional angle: H4-C4-C5-H5 -177.2(0)°]. A perspective drawing for compound (413) is presented above in Figure 4.8 (corresponding atomic coordinates are given in Section 5.8, Table 10).

4.2.2 The isolation of compounds (403) and (405)

The residue from the crystallization above (Section 4.2.1.1), was partitioned into pentane soluble and pentane insoluble fractions, by stirring the mixture overnight in pentane. This effected a very efficient separation of the two aromatic nitro compounds (403) and (405), as they are readily soluble in pentane, whereas the other compounds are not. They were purified by chromatography on a Chromatotron silica gel plate, using petroleum ether/ ether solvent mixtures, and were identified by comparison of their spectroscopic data, with the corresponding literature data.



Compound (403)



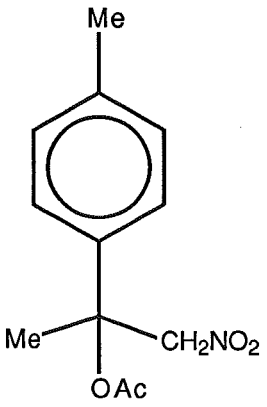
Compound (405)

4.2.3 Separation of the pentane insoluble compounds

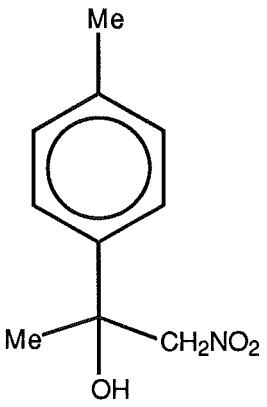
The pentane insoluble fraction obtained from the partition above (Section 4.2.2) still contained compounds (414), (415), (416), (417), (418), (419),

(420) and (421). These eight compounds were separated and purified by a combination of low temperature chromatography, h.p.l.c, and fractional crystallization techniques.

4.2.3.1 The two aromatic compounds (414) (3%) and (415) (3%) were finally purified by h.p.l.c. methods (normal phase, hexane/dichloromethane solvent mixtures), and were subsequently identified on the basis of their respective spectroscopic data. High resolution mass spectrometry yielded molecular formulae for the two compounds, and infrared spectroscopy revealed the existence of nitro groups in both compounds, in addition to a carbonyl function in compound (414) and a hydroxyl function in compound (415).



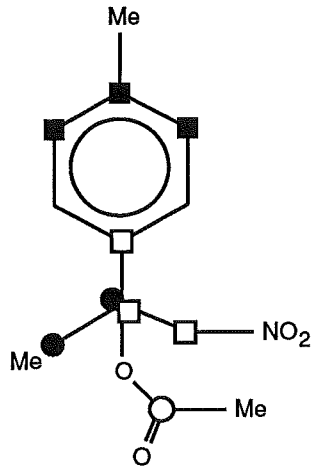
Compound (414)



Compound (415)

N.m.r. spectroscopy however, proved to be the most valuable spectroscopic technique in elucidating the overall structure for the two compounds. The ^1H n.m.r. spectra of both compounds show aromatic regions (c. δ 7-8 ppm) characteristic of a 1,4 disubstituted benzene, displaying an AB quartet system (*J* c. 8 Hz) with a relative integral for 4 hydrogens. Furthermore, both compounds have an additional AB quartet system in the δ 4-5 ppm range, consistent with the existence of a nitro-alkyl group.[88,89] Final confirmation of the structures, linking all the above individual pieces of spectroscopic information, was achieved by using the 2-D n.m.r. pulse sequence XCORFE,[63] which displays correlations for two and three bond C-H couplings (see Section 1.4). For compound (414), the correlations observed are summarized in Figure 4.9, below.

The three different methyl groups appear as three singlets in the ^1H n.m.r. spectrum at chemical shifts of δ 1.95, 2.13, and 2.34 ppm respectively, and



Connectivities

- ■ 1-Me hydrogens
- ❑ 4-(1-Me) hydrogens
- ● nitromethyl hydrogens
- ○ acetate-Me hydrogens

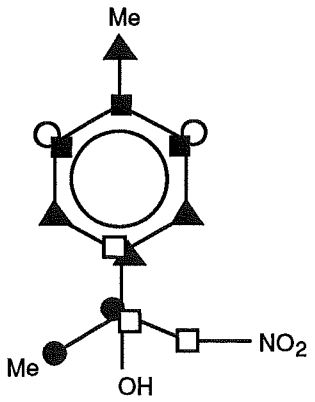
Figure 4.9 XCORFE connectivities for compound (414).

the XCORFE connectivities from these three positions reveal a great deal about the carbon framework of the compound. The methyl resonance at δ 2.13 ppm displays a single, very strong correlation to the carbonyl carbon, quite characteristic of an acetate grouping. Further, the δ 2.34 ppm methyl group displays only two correlations, both to carbons in the aromatic ring, confirming it as an isolated aromatic methyl group. This information, when considered in conjunction with the known 1,4-disubstitution pattern of the compound, suggests that all the other substituents are bound either directly, or indirectly at C4, the ring position *para* to this methyl group. The existence of strong connectivities from both the methylene hydrogens, and the δ 1.95 ppm non-aromatic methyl hydrogens, to a single non-protonated carbon, and then further through to C4 in the aromatic ring, confirm the arrangement of this remaining methyl group and the nitromethyl group, and result in the proposed 4-(1-acetato-1-methyl-2-nitroethyl) substituent, illustrated above.

Final confirmation of the structure comes from the fragmentation pattern observed in the high resolution mass spectrum for the compound, it also being consistent with the above structure. In particular, strong signals appear for the molecular fragments resulting from (i) loss of nitrogen dioxide ($C_{12}H_{15}NO_2$, *m/z* 191.1), and (ii) a subsequent loss of $CH_2C{=}O$ from the acetate group ($C_{10}H_{13}O$, *m/z* 149.1). The base peak in the mass spectrum ($C_9H_{11}O$, *m/z* 135.1) is probably due to a protonated *p*-methyl-acetophenone molecule, and a further signal at *m/z* 91.1 is undoubtedly due to the PhMe (C_7H_7) fragment.

For compound (415), the XCORFE correlations are presented below (Figure 4.10). The connectivities observed, were in general very similar to those

observed for the acetate (414), and the line of reasoning followed in assigning the structure was identical.



Connectivities

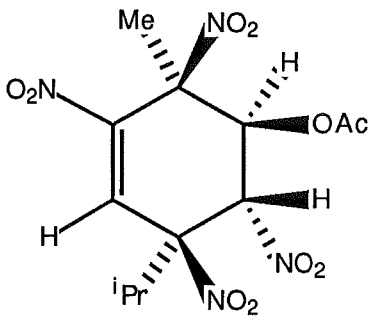
- ■ 1-Me hydrogens
- ❑ 4-(1-Me) hydrogens
- ● nitromethyl hydrogens
- ○ H3 and H5
- ▲ H2 and H6

Figure 4.10 XCORFE connectivities for compound (415).

The connectivities observed, when considered in combination with the other spectroscopic information, result in the structure proposed above, analogous to compound (414) except for the replacement of the acetate group by a hydroxyl function. The high resolution mass spectral fragmentation pattern, was once again in accord with the above structure. Not surprisingly, the fragmentation patterns for the two compounds (414) and (415) are closely similar, and the major signals observed at *m/z* 135.1 ($C_9H_{11}O$) and *m/z* 91.1 (C_7H_7) in the mass spectrum of compound (414) also appear in the mass spectrum of compound (415). The base peak in the spectrum of compound (415) however, appears at *m/z* 119.1 (C_8H_7O), due to the fragment MePhCO.

4.2.3.2 Compound (416) (1%), was isolated only on one occasion, and then as a slightly contaminated (*c.* 80% pure) 4mg h.p.l.c. fraction. Its structural assignment is based on (i) its n.m.r. spectroscopic data, and (ii) comparisons of that data, with similar data for related compounds, in particular compounds (410), (413) and (420).

The existence of the acetate group is suggested by the presence of a δ 2.11 ppm sharp singlet in the ^1H n.m.r. spectrum, which shows no n.O.e. correlations with any other protons [as was observed for the acetate group of the other acetate compound (413)]. Although compound (416) retains the now familiar 11.5 Hz coupling constant between



Compound (416)

H4 and H5, analogous to that observed for the cyclohexenes (410), (411), (412) and (413) (Section 4.2.1) discussed above, the n.O.e. experiments show a quite different set of proton-proton interactions.

These results can only be rationalized by an appropriate alteration of the stereochemical relationship between the chiral atoms. For the cyclohexenes discussed above, the largest n.O.e. effects were observed between (i) the 6-methyl group and H5, and (ii) the two distinct *iso*-propyl methyl groups and H2 and H4 respectively.

For compound (416) the large correlation between the 6-methyl group and H5 remains, but the two *iso*-propyl methyl groups now display strong correlations with H2 and H5 respectively (Figure 4.11). This can be explained only by proposing a change of stereochemistry at C3, *i.e.* compound (416) is the C3-epimer of the previous tetranitro acetate (413).

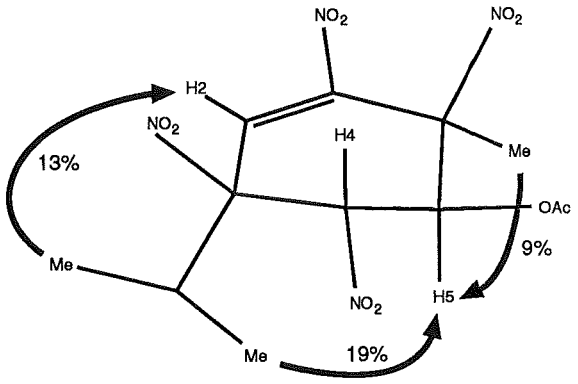


Figure 4.11
N.O.e. correlations for compound (416).

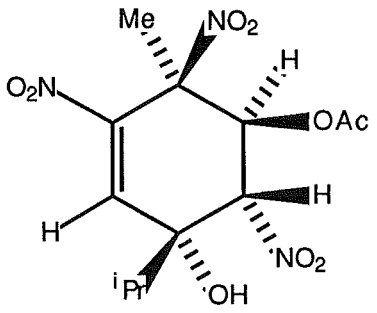
Confirmation of this assignment can be obtained by comparing the ^{1}H n.m.r. spectroscopic data for the two sets of C3 epimers: compounds (410) and (420) [compound (420) is discussed in detail later in this section], and the two tetranitro acetates (413) and (416). A summary of their respective ^{1}H n.m.r. chemical shift data is presented in Figure 4.12.

	NITRATES		ACETATES	
Compound	**(410)**	**(420)**	**(413)**	**(416)**
iPr-Me	1.19 ppm	1.16	1.16	1.12
iPr-Me	1.29	1.30	1.25	1.28
6-Me	2.07	2.01	1.98	1.91
iPr-H	3.18	2.94	3.13	2.94
H4	5.68	5.76	5.66	5.68
H5	6.01	6.19	5.96	6.14
H2	7.42	7.65	7.40	7.67

Figure 4.12 Selected ^{1}H n.m.r. chemical shift values (ppm).

The chemical shift displacements observed in moving from the *r*-3, *c*-4, *t*-5, *t*-6 configuration [compounds (410) and (413)] to the *r*-3, *t*-4, *c*-5, *c*-6 configuration [compounds (420) and (416)] (*i.e.* from one compound to its C3-epimer), are almost identical for the two sets of epimers. In particular, a large downfield shift (Δ 0.27 ppm) of the H2 resonance is observed between compound (413) and compound (416), and this is similar to the chemical shift difference (Δ 0.23 ppm) observed between the H2 resonances of compounds (410) and (420). The other changes of chemical shift are somewhat less spectacular, but all the trends observed upon alteration of the stereochemistry at C3 for the two tetranitro nitrates (410) and (420), are replicated in the case of the two tetranitro acetates (413) and (416). As single crystal X-ray structure analyses have been conducted for the two tetranitro nitrates (410) and (420), and given the very close n.m.r. spectroscopic similarities discussed above, the structure of the tetranitro acetate (416) appears to be certain.

Compound (417) (1%) was isolated by normal phase h.p.l.c. methods, and was subsequently recrystallized from hexane/ dichloromethane. The ^{1}H and ^{13}C n.m.r. spectra suggest a structure closely related to the cyclohexenes isolated previously, and n.O.e. experiments display correlations almost identical to those observed for compounds with the *r*-3, *c*-4, *t*-5, *t*-6 stereochemistry, *i.e.* compounds (410), (411), (412) and (413).



Compound (417)

The infrared spectrum displays clear OH and C=O stretching absorptions. All of these facts point to the structure being as illustrated above, and indeed on the basis of this spectroscopic information alone, the structure could be assigned with confidence. As insufficient material of compound (417) was isolated to make elemental analysis practicable, single crystal X-ray structure analysis was used as the simplest, and most definitive way of confirming the overall structure. A perspective diagram of the structure is presented in Figure 4.13, below (corresponding atomic coordinates are listed in Section 5.8, Table 11).

The single crystal X-ray analysis revealed that in the solid state the alicyclic ring exists in a flattened half chair conformation [torsional angles: C1-C2-

C3-C4 18.3(3)°; C2-C1-C6-C5 5.3(4)°]. The expected *anti*-coplanarity of H4 and H5 is verified by the torsional angle H4-C4-C5-H5 -174.9(0)°.

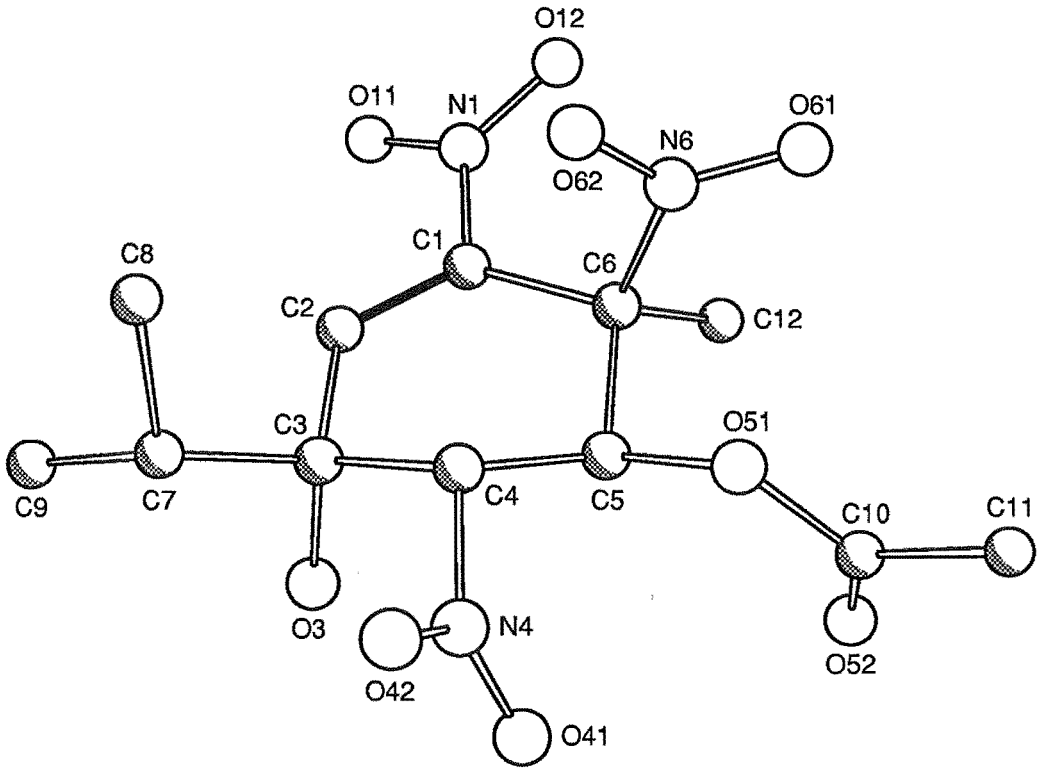
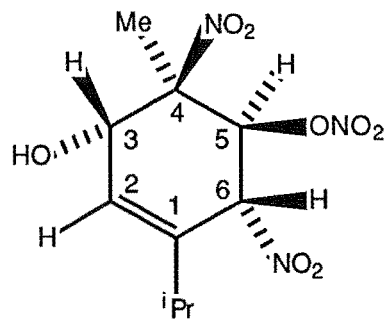
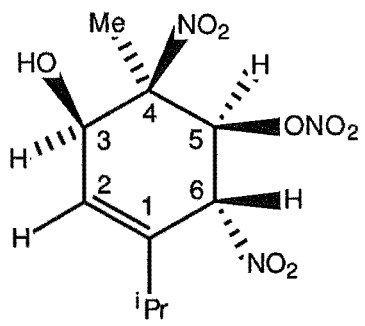


Figure 4.13 Perspective diagram of compound (417). Double bond shown in black.

4.2.3.3 Compounds (418) and (419) were isolated by normal phase h.p.l.c. separation of a fraction initially obtained from the crude chromatographic separation by Chromatotron. The very close similarity of their ^{13}C n.m.r. spectra, and the existence, in both their ^{1}H n.m.r. spectra, of four downfield proton signals, as opposed to the previously observed three, suggested, at the very least, some structural similarities between the two compounds. Noticeably, the 11-12 Hz coupling constant between H5 and H6 has fallen to 5.7 Hz for compound (418) and 7.5 Hz for compound (419).



Compound (418)



Compound (419)

Both compounds display different, but complex coupling patterns for the downfield protons in the ^{1}H n.m.r. spectra. These patterns are summarized in Figure 4.14, below.

	H2	H3	H5	H6	H7	OH
H2	■■	4.4 Hz		✓	✓	
H3	4.4 Hz	■■		✓		
H5			■■	5.7 Hz		
H6	✓	✓	5.7 Hz	■■	✓	
H7	✓			✓	■■	
OH						■■

	H2	H3	H5	H6	H7	OH
H2	■■	✓		✓	✓	
H3	✓	■■		✓	✓	10.6 Hz
H5			■■	7.5 Hz		
H6	✓	✓	7.5 Hz	■■	✓	
H7	✓	✓		✓	■■	
OH		10.6 Hz				■■

Figure 4.14 ^{1}H n.m.r. couplings for compounds (418) (top), and (419) (bottom).
✓ indicates a small coupling, in the order of 1-2 Hz.
H7 refers to the *iso*-propyl group's hydrogen atom.

The n.O.e. experiments conducted for the two compounds, once again displayed a close similarity of results, both showing strong correlations between (i) the *iso*-propyl methyls and H2 and H6, and (ii) the 4-methyl group and H5 and H3. For compound (419) however, an additional, strong, cross-ring correlation is observed between H5 and H3, and this is absent in the case of compound (418). For more ready appreciation of the implications of the above results, it is advantageous to look first at the results of the single crystal X-ray structure analysis performed on compound (419). A perspective diagram is presented below in Figure 4.15 (corresponding atomic coordinates are given in Section 5.8, Table 12).

In the solid state, compound (419) exists in a flattened half chair conformation [torsional angles: C1-C2-C3-C4 -18.9(5)°; C2-C1-C6-C5 -10.9(4)°], in which H5 and H6 are now slightly removed from an *anti*-coplanar arrangement [torsional angle: H5-C5-C6-H6 165.8(0)°]. The C3-substituents

are close to being staggered with respect to the C4-methyl group [torsional angles: C10-C4-C3-O3 -64.0(3)°; C10-C4-C3-H31 52.4(2)°], but of the two groups, the hydroxyl group lies much closer to the plane of the double bond [torsional angle: H2-C2-C3-O3 31.9(4)°]. Indeed the hydrogen H31, is in an almost "flagpole" orientation [torsional angle: H2-C2-C3-H31 -84.2(1)°]. The hydrogen atom of the hydroxyl group H32, sits in a somewhat *anti*-coplanar arrangement to H31 [torsional angle: H32-O3-C3-H31 155.6(0)°], and this is reflected in the 10 Hz coupling constant between these two atoms in the ^{1}H n.m.r. spectrum.

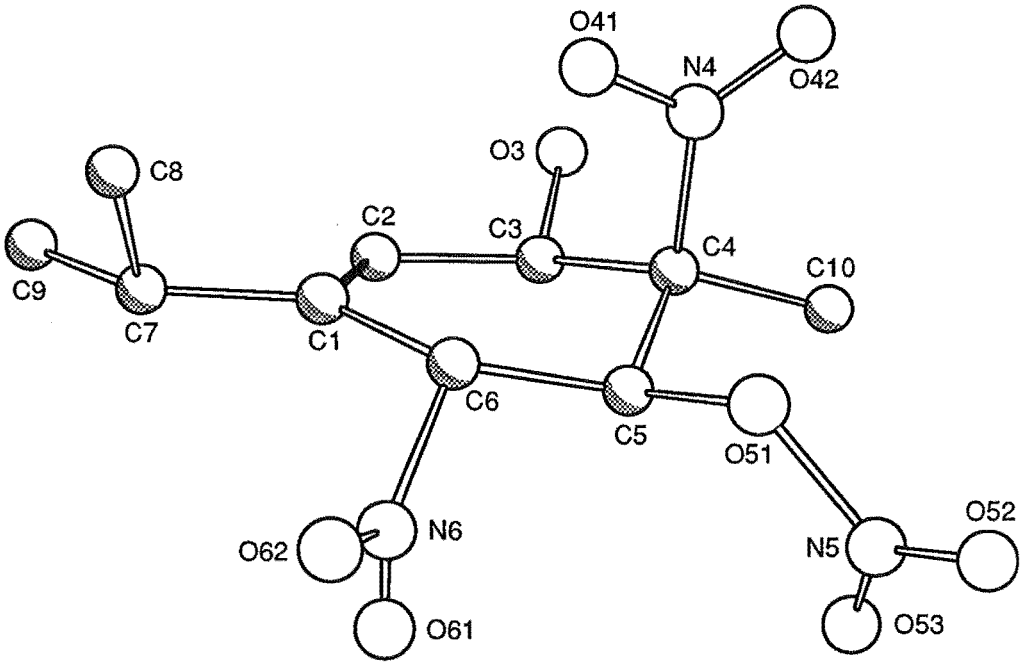


Figure 4.15 Perspective diagram of compound (419). Double bond shown in black.

With the information obtained from this single crystal X-ray structure analysis, it now becomes somewhat simpler to explain some of the trends and phenomena reported above.

(i) The positioning of the double bond between the *iso*-propyl substituted carbon and C2, is in contrast to what was observed for the previously isolated cyclohexenes, where the double bond linked what is labelled C2 and C3 in the present two compounds. This change of location of the double bond is directly reflected in the loss of *anti*-coplanarity between H5 and H6. Indeed, if it is assumed that the alicyclic ring conformations are approximately the same for all the cyclohexenes, then the closest approach to *anti*-coplanarity for compounds (418) and (419)

should be between the two axial substituents at C4 and C5. This is confirmed for structure (419) by the torsional angle N4-C4-C5-H5 180.0(0)°.

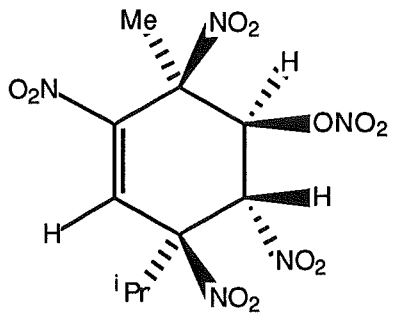
(ii) The lack of a cross-ring n.O.e. correlation between H3 and H5 in compound (418) suggests that the stereochemistry at either C3 or C5 is different to that observed for compound (419). As the C3 substituents in compound (419) are approximately staggered with respect to the 4-methyl group (see discussion above), and if we assume that altering the stereochemistry at C3 will have little effect on the alicyclic ring conformation, then such an alteration of stereochemistry at C3 should result in a loss of the cross-ring n.O.e. correlation observed in compound (419), but show little change in the magnitude of the n.O.e. enhancements observed upon irradiation of the 4-methyl resonance. This is indeed what is observed for compound (418). The possibility that compound (418) could be the C5-epimer of compound (419) seems less likely, as the required alteration of C5 stereochemistry would result in a large decrease in the H4, H5 coupling, due to the change in the H4-C4-C5-H5 torsional angle.

(iii) If we assume, as in (ii) above, that altering the stereochemistry at C3 will not drastically alter the ring conformation, then the variations in coupling patterns between the two compounds can be rationalized. In the ^{1}H n.m.r. spectrum of compound (419) H2 appears as a *pseudo*-quartet with a coupling constant (*J*) of 1-2 Hz. This arises from the coupling of H2 with H3, H6, and H7 (the *iso*-propyl hydrogen), all with similar coupling constants. The reason for the apparently low vicinal coupling between H2 and H3 can be explained by the torsional angle between the two groups (H2-C2-C3-H3) of -84.2°, close to the angle where vicinal coupling is at its minimum. In contrast, the H2 resonance for compound (418) appears as an apparent doublet of triplets, with the main coupling of 4.4 Hz between H2 and H3, and minor couplings to H6 and H7. This is consistent with a narrowing of the H2-C2-C3-H3 torsional angle. If the above assumption is valid then the value of this torsional angle can be approximated by the torsional angle H2-C2-C3-O3 for compound (419), 31.9(4)°. Although this angle is still far removed from the angle for maximum coupling to be observed, it is sufficient to account for the dramatic increase in the value of the H2,H3 coupling constant found in compound (418). The differing C3-stereochemistry between the two compounds is also presumably sufficient to alter the H32-O3-C3-H31 torsional angle, thus explaining the absence in

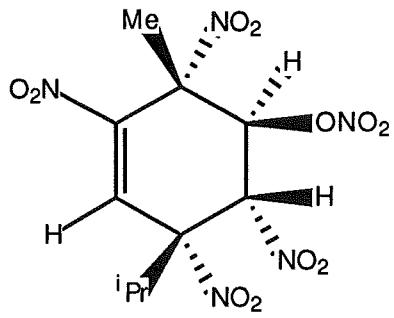
compound (418) of the large 10 Hz coupling, observed in compound (419), between H3 and the OH proton.

Final evidence for the assignment of structure (418) was obtained upon the isolation and characterization by single crystal X-ray structure analysis of the stereochemically equivalent nitro derivative (replacement of the OH group by a nitro group) of compound (418) (see Section 4.5.1.1). Compound (434) displays identical n.O.e. correlations and coupling patterns between the downfield protons, to those observed for compound (418).

4.2.3.4 The remaining two compounds, (420) (4%) and (421) (1%), were isolated by a combination of silica gel chromatography, normal phase h.p.l.c. methods using hexane/dichloromethane as the eluting solvent, and fractional crystallization. The compounds have the same molecular structure, differing only in the relative stereochemistry at the four chiral centres. Indeed, they are both closely related to compound (410), all three compounds being 1,3,4,6-tetranitro-5-nitrato-cyclohexenes.



Compound (420)



Compound (421)

The structures of compounds (420) and (421) were determined by single crystal X-ray structure analyses. Compound (421), in particular, represents only a very small percentage of the total reaction product mixture, and X-ray structure analysis provided the simplest method for structure determination from the small sample of pure compound available. Although X-ray analysis confirmed the chemical structures for the two compounds, n.O.e. experiments gave strong indications of the relative stereochemistries, and the X-ray analyses simply confirmed the tentative stereochemical assignments made on the basis of these n.O.e. results. Figure 4.16 displays a comparison of the n.O.e. correlations for the three stereoisomeric tetranitro nitrates (410), (420) and (421).

Compound		(410)	(420)	(421)
Stereochemistry		*r*-3,*c*-4,*t*-5,*t*-6	*r*-3,*t*-4,*c*-5,*c*-6	*r*-3,*c*-4,*t*-5,*c*-6
n.O.e. correlations				
from	6-methyl	H5 (16%)	H5 (10%)	H4 (10%)
	iPr-Me (1)	H2 (16%)	H2 (12%)	H2 (16%)
	iPr-Me (2)	H4 (16%)	H5 (16%)	H4 (17%)

Figure 4.16 Selected n.O.e. correlations for the three tetranitro nitrates.

Strong n.O.e. correlations between groups on adjacent carbons will exist only if the two substituents in question are close to one another in space, *i.e.* are in a *cis* relationship. Hence from the results above, it is certain that there are *cis* relationships between the 6-methyl group and H5 for compounds (410) and (420), and between the *iso*-propyl group and H4 for compounds (410) and (421). By default therefore, the relationships between the 6-methyl group and H5 in compound (421), and the *iso*-propyl group and H4 in compound (420) must be *trans* relationships. These indications, when coupled with the known existence of strong H4, H5 couplings in the ^{1}H n.m.r. spectra of all three compounds, were sufficient to allow reasonably confident assignment of the structures of compounds (420) and (421).

The single crystal X-ray structure analysis of compound (420) confirmed the structural assignment suggested on the basis of the n.O.e. results. A perspective diagram for the structure is presented below (Figure 4.18), and corresponding atomic coordinates are tabulated in Section 5.8, Table 13.

In the solid state, the crystallographic asymmetric unit for compound (420) consists of two chemically equivalent, but crystallographically distinct molecules. Superposition of the two molecules reveals no gross differences of any chemical significance between the two molecules (Figure 4.17).

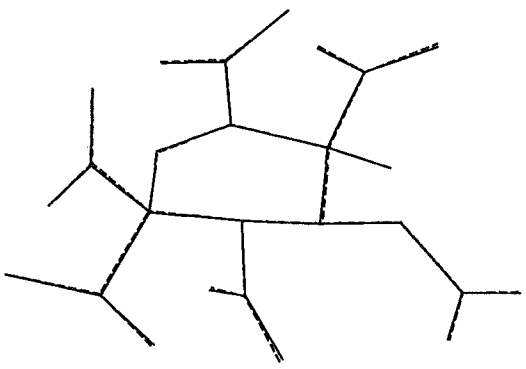


Figure 4.17 Superposition of two molecules of compound (420).

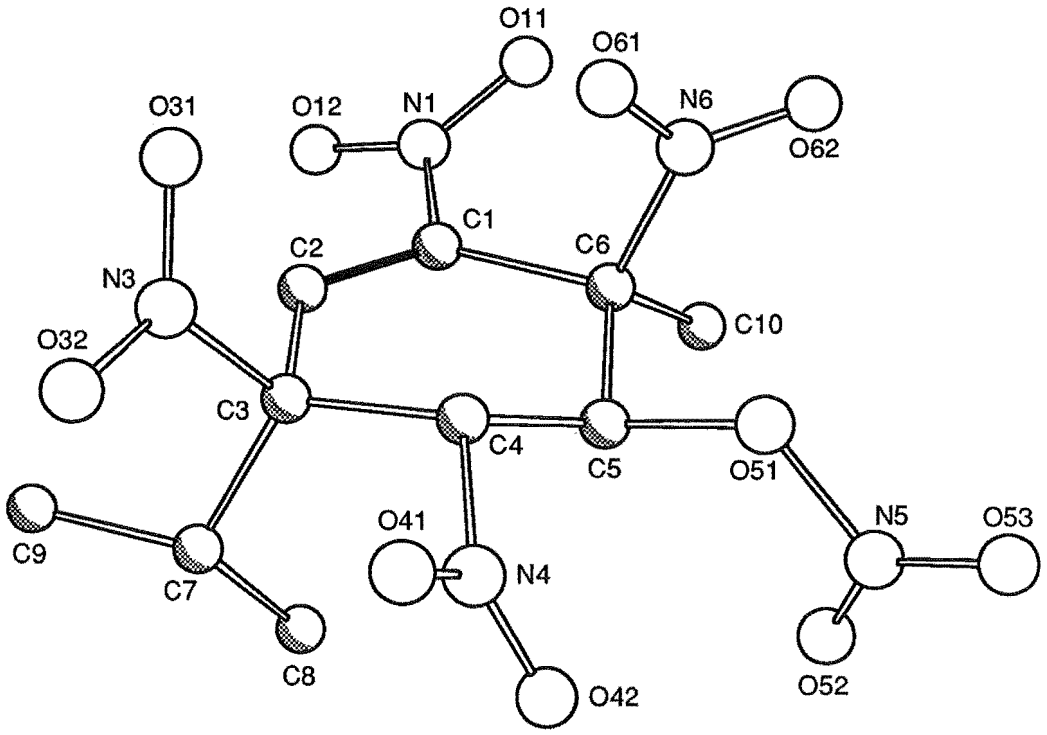


Figure 4.18 Perspective diagram of compound (420). Double bond shown in black.

Both of the independent molecules exist in flattened half chair conformations [torsional angles: molecule 1, C1-C2-C3-C4 13.7(4)°, C2-C1-C6-C5 12.2(4)°; molecule 2, C1'-C2'-C3'-C4' -11.3(4)°, C2'-C1'-C6'-C5' -11.1(4)°]. The change of stereochemistry at C3 with respect to compound (410), displaces the C3-substituents toward a staggered arrangement with respect to the double bond [torsional angles: molecule 1, H2-C2-C3-N3 -54.7(2)°; H2-C2-C3-C7 62.1(2)°; molecule 2, H2'-C2'-C3'-N3' 57.6(2)°; H2'-C2'-C3'-C7' -59.3(3)°], compared with compound (410), where the C3-nitro group occupies an almost "flagpole" orientation [torsional angles for (410): H2-C2-C3-N3 86.9(2)°; H2-C2-C3-C7 -32.4(1)°]. Notwithstanding the above, H4 and H5 remain very close to *anti*-coplanar [torsional angles: molecule 1, H4-C4-C5-H5 -177.7(0)°; molecule 2, H4'-C4'-C5'-H5' 177.6(0)°].

Compound (421) is the most polar compound in this series of cyclohexene derivatives, being the last compound eluted from both the chromatographic separation on silica (eluted in 5% methanol in ether), and the normal phase h.p.l.c. separations. As a consequence of this polarity, it is relatively insoluble, and it was this property which enabled the isolation of a small amount of pure, crystalline material, fractionally crystallized from a rather impure fraction which eluted from the Chromatotron. The structure of the compound was determined by single crystal X-ray structure analysis,

although as mentioned above (see Figure 4.16 and discussion thereafter), the n.O.e. experimental data provided strong evidence for the same structure. A perspective diagram of the compound is presented below (Figure 4.19), and corresponding atomic coordinates are listed in Section 5.8, Table 14.

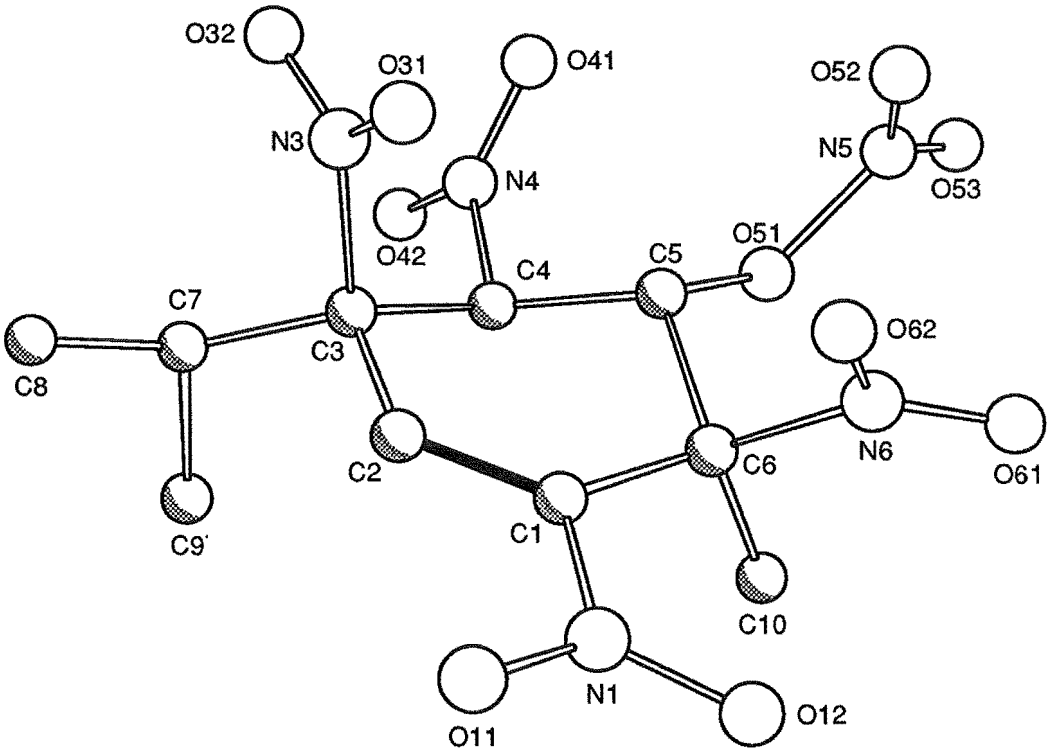


Figure 4.19 Perspective diagram of compound (421). Double bond shown in black.

In the solid state the compound exists in a flattened half chair conformation [torsional angles: C1-C2-C3-C4 14.6(2)°; C2-C1-C6-C5 16.9(2)°]. The C6-substituents are approximately staggered with respect to the C1-nitro group [torsional angles: N1-C1-C6-C10 69.3(2)°; N1-C1-C2-N6 -52.9(2)°], as was observed for the C3-epimer of this compound, the tetranitro nitrate (410). The altering of stereochemistry at C3 therefore, appears to have very little effect on the alicyclic ring conformation. Not surprisingly then, H4 and H5 retain their nearly *anti*-coplanar relationship [torsional angle: H4-C4-C5-H5 -169.8(0)°].

One feature of the ^{1}H n.m.r. spectrum of compound (421) worthy of note, is the dramatic upfield shift (Δ 0.57 ppm) of the H4 resonance, with respect to compound (410). This can only be an effect of the changed stereochemistry at C3, and indeed, if one compares the perspective diagrams for the two epimers (Figure 4.20), this phenomenon can be rationalized. In the

structure of compound (410), H4 and the C6-nitro group are in a *cis* relationship, and the two groups exist relatively close to one another. As a consequence, the H4 atom is deshielded by the proximate C6-nitro group. In moving to structure (421), where the stereochemistry at C3 is reversed with respect to compound (410), this strongly deshielding nitro group is replaced by a methyl substituent. The effective magnetic shielding experienced by the H4 atom in compound (421), is thus markedly different from that experienced in compound (410), and hence, a large change in the ^{1}H n.m.r. chemical shift for H4 is observed.

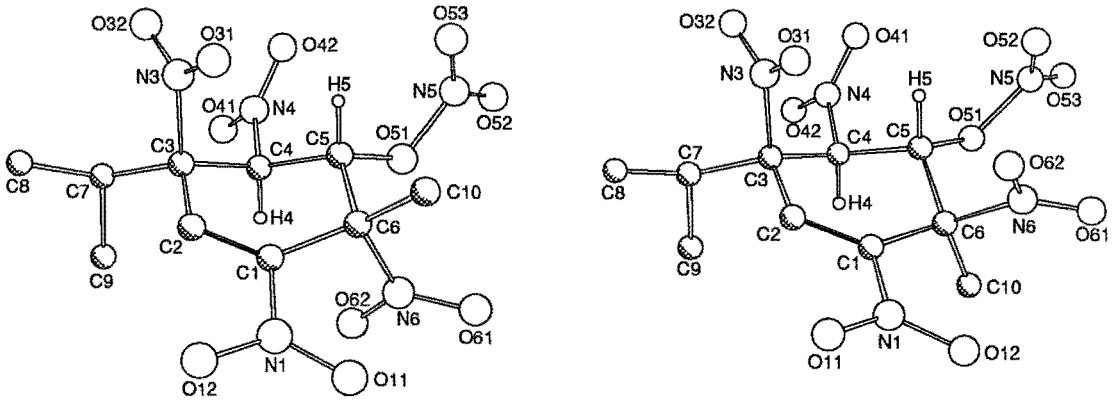
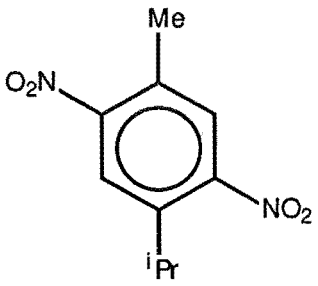


Figure 4.20 Comparison of the structures of compound (410) (left), and compound (421) (right).

4.2.3.5 A further compound (422) was isolated on numerous occasions during the separation of the eight compounds reported above. This compound (422) was not present in the initial reaction product mixture, and is believed to be a decomposition product derived from the genuine reaction products. The structure of the material is based on its ^{1}H n.m.r. and i.r. spectroscopic data, and on the close similarity of the melting point recorded for compound (422), and the literature value[81] reported for 2,5-dinitro-*p*-cymene.



Compound (422)

4.2.4 Control experiments

Control experiments were performed by treating separately, compounds (403), (410) and (412) with excess nitrogen dioxide in acetic anhydride for

24 hours. In all three experiments, an essentially quantitative recovery of the pure compound was observed, demonstrating (i) that all of these compounds must be final products of reaction, and (ii) that none of them can be involved as transient intermediates in the overall reaction to final products.

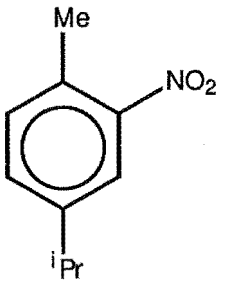
4.3 DISCUSSION: THE NITRATION OF *P*-CYMENE IN CH_2Cl_2

The reaction of *p*-cymene with excess nitrogen dioxide in dichloromethane solution was investigated to determine what influence, if any, the acetic anhydride solvent was having in directing the course of the reaction discussed in Section 4.2.

Reaction of *p*-cymene (401) with excess nitrogen dioxide in dichloromethane solution for 24 hours gave a crude product, shown (^{1}H n.m.r.) to be a mixture (*c.* 5:3:6:33:12:6:11) of compounds (403), (405), (415), (423), (424), (425) and (426) respectively. These compounds were generally separated by chromatography on silica, using a Chromatotron, although for compounds (424), (425) and (426) final purification was achieved by h.p.l.c. on a normal phase cyano-propyl column. The yields quoted below, and in the Experimental Section, were estimated from the respective integrals in the ^{1}H n.m.r. spectrum of the crude product mixture, and do not reflect the amount of pure material isolated.

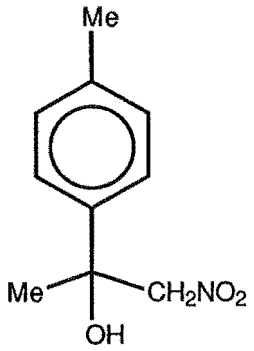
4.3.1 Isolation and identification of products

The three compounds (403) (5%), (405) (3%) and (415) (6%) had been previously isolated and identified from the product mixture of the reaction between *p*-cymene and nitrogen dioxide in acetic anhydride (see Section 4.2). Separation of these compounds was achieved by silica gel chromatography using a Chromatotron. Subsequent comparison of their spectroscopic (n.m.r., i.r.) data, with similar data from authentic samples, showed them to be identical in all respects to the products obtained from the acetic anhydride reaction.



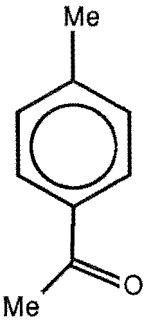
Compound (403)

Compound (405)



Compound (415)

4.3.1.1 The major product of reaction, *p*-methylacetophenone (423) (33%) was also eluted from the silica gel Chromatotron plate as a pure compound. Its structural assignment is based on (i) information from the high-resolution mass spectrum, including the accurate mass of the parent ion (*m/z* 135.081 for M+H), and the mass spectral fragmentation pattern, (ii) the n.m.r. and i.r. spectroscopic data, and (iii) comparisons of these spectroscopic data with the corresponding literature data.



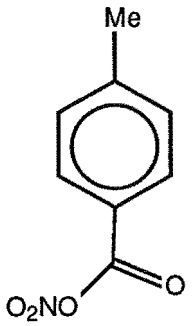
Compound (423)

4.3.1.2 The remaining three compounds were eluted from the Chromatotron silica gel plate in the elution order: compound (426) (11%), compound (424) (12%) and compound (425) (6%). However, for all these compounds, pure samples could not be obtained by chromatography on silica, and further purification, using normal phase h.p.l.c. techniques, was necessary.

Compounds (424) and (425) proved to be particularly difficult to purify, as they eluted from the Chromatotron silica gel plate, and the normal phase h.p.l.c. column with almost identical retention times. Ultimate separation of the two compounds was achieved by a room-temperature vacuum distillation, as it was found that compound (424) was quite volatile under these conditions.

The sample of the mixed anhydride (424) thus obtained was almost pure, although it remained slightly contaminated with traces of compound (425). The structural assignment for compound (424) remains uncertain, as confirmation of the molecular formula by high-resolution mass spectrometry has proved difficult.

Strong signals at *m/z* 119 (MePhC=O) and *m/z* 136 (MePhCOOH) strongly support the basic molecular framework illustrated, but the lack of any signals at higher mass values, means confirmation of the nitrate group is not possible. Indeed, the major evidence for the nitrate group is the existence, in the i.r. spectrum, of three strong absorptions at 1630, 1283 and 857 cm^{-1}, these absorption bands being characteristic of a nitrate group.



Compound (424)

The n.m.r. spectroscopic data provides additional support for the carbon skeletal framework illustrated above. Both the ^{1}H and ^{13}C n.m.r. chemical shift values are consistent with the proposed structure. Furthermore, the two and three bond C-H correlations identified using the two-dimensional pulse sequence XCORFE[63] (see Figure 4.21), are also in accord with the proposed structure.

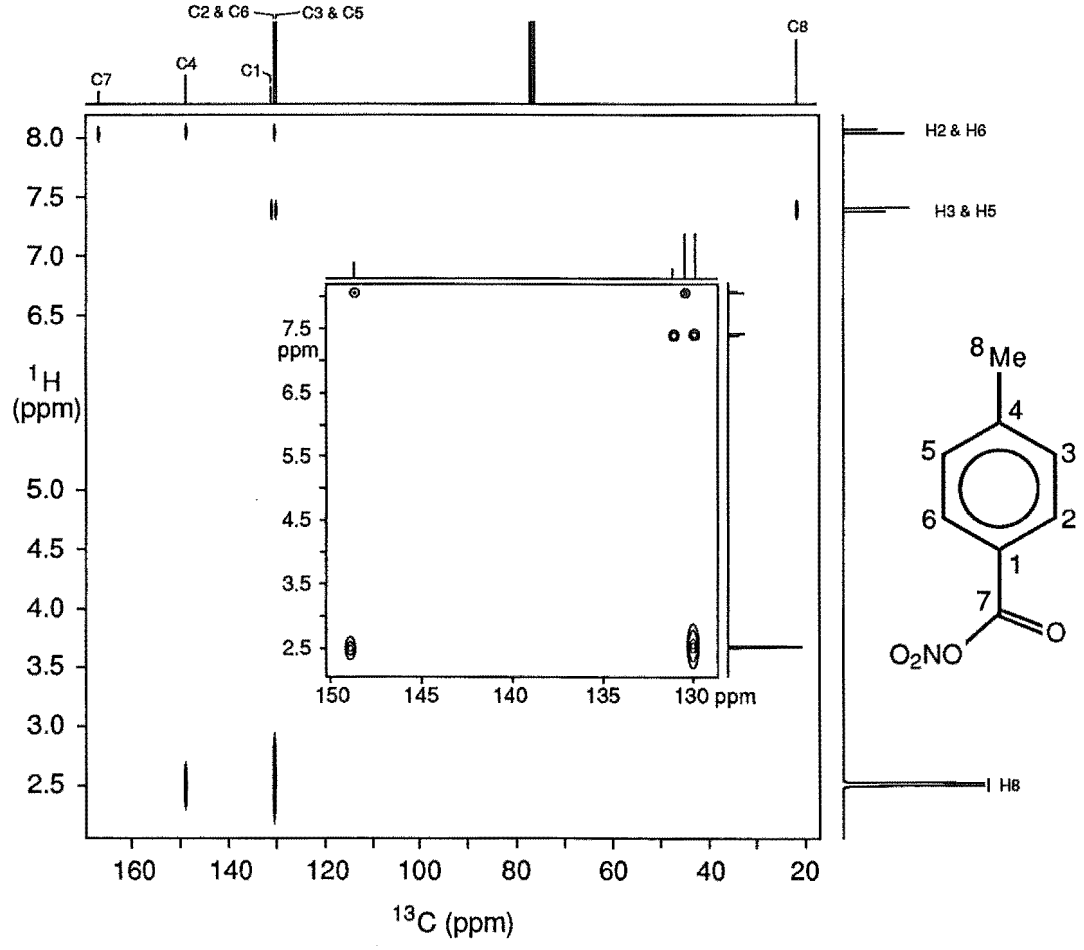
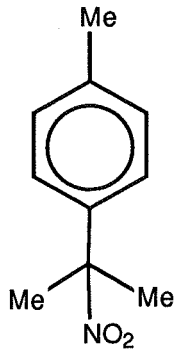


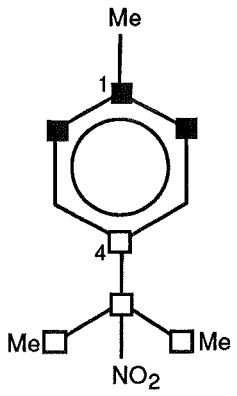
Figure 4.21 Contour plots from an XCORFE experiment conducted for compound (424).

The residue from the above vacuum distillation, used to isolate a sample of compound (424), yielded an almost pure sample of compound (425). The structural assignment for this compound (see Figure at right) is based on its n.m.r. and i.r. spectroscopic data, and on comparisons of these data with the corresponding literature data.



Compound (425)

In particular – (i) the ^1H n.m.r. and i.r. spectroscopic data for the compound isolated from this reaction, are closely similar to those reported by Kozyrod *et al.* for compound (425) generated by C-arylation of 2-nitropropane;[90] (ii) all the carbon chemical shift values are consistent with the proposed structure, including the nitro-substituted tertiary carbon atom (δ 89.65 ppm); (iii) the existence, in the aromatic region of the ^1H n.m.r. spectrum, of an ABq system with a relative integral of four hydrogens, is indicative of the 1,4-disubstituted benzene structure; (iv) the i.r. spectrum shows typical nitro group absorptions at 1542 and 1355 cm^{-1}; and (v) the higher field portion of the ^1H n.m.r. spectrum, in particular the singlet at δ 1.81 ppm with a relative integral of six hydrogens, can only be accounted for satisfactorily by the symmetrical (1-methyl-1-nitroethyl) substituent postulated.



Connectivities

■ 1-Me hydrogens

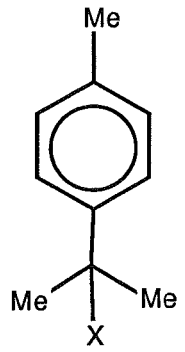
❑ 4-(1-Me) hydrogens

The two-dimensional n.m.r. pulse sequence XCORFE provides additional evidence for the structural assignment illustrated above. The two and three bond C-H correlations thus observed (Figure 4.22) are in accord with the above structure.

Figure 4.22 XCORFE results for compound (425).

4.3.1.3 Compound (426) was purified by h.p.l.c. techniques, and was eluted from the normal phase cyano-propyl h.p.l.c. column in hexane/dichloromethane (99:1) solution. The fraction thus obtained was

essentially pure compound (426). From the ^1H n.m.r. spectrum, it is obvious that compound (426) is structurally closely related to compound (425). Both compounds have very similar, relatively simple n.m.r. spectra, consisting of (i) a downfield ABq system (with a relative integral of four hydrogens) due to the aromatic hydrogen atoms, and (ii) two singlet signals at higher field, with a relative integral ratio of 3:6.



Compound (426)

However, despite being able to assign the structural skeleton for compound (426), the nature of the substituent "X" remains uncertain. The evidence available – (i) an i.r. spectrum with strong absorptions at 1566, 1328 and 1067 cm^{-1}, (ii) information from the mass spectrum, and (iii) a carbon chemical shift value of δ 92.15 ppm for the X-substituted tertiary carbon atom, 2.5 ppm downfield of the corresponding value for compound (425) – is not sufficient to allow unequivocal assignment of the substituent "X".

4.3.2 Reaction pathways in the nitration of *p*-cymene in CH_2Cl_2

On the basis of the compounds isolated from the reaction of *p*-cymene with nitrogen dioxide in dichloromethane, it is clear that the reactions involved in forming these compounds, are quite different to those seen in the corresponding reaction of *p*-cymene in acetic anhydride. The absence of any cyclohexene derivatives (which account for over half of the products observed in the acetic anhydride reaction) in the product mixture, and the very low yield of 2-nitro-*p*-cymene (403) (5%), suggest that the aromatic ring of *p*-cymene is actually relatively inert to attack by the nitrogen dioxide radical. Indeed, with the exception of 2-nitro-*p*-cymene (403), all the products isolated from the reaction in dichloromethane, are products resulting from modification of the *iso*-propyl group.

4.3.2.1 The initial step in the formation of these compounds probably involves a hydrogen atom abstraction, by a nitrogen dioxide radical, of the *iso*-propyl hydrogen atom, yielding the relatively stable, resonance stabilized, tertiary radical (427) (Figure 4.23, below). Once radical (427) forms, subsequent reaction with nitrogen dioxide probably occurs comparatively

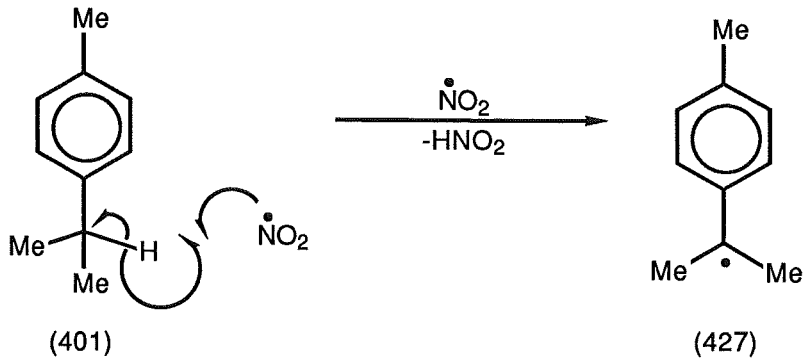


Figure 4.23 Hydrogen abstraction of the *iso*-propyl hydrogen atom.

rapidly, as the radical (427) will be quite susceptible to attack by other unpaired electron (upé) species. It is interesting to note that, although resonance stabilization in radical (427) will result in some upé spin density

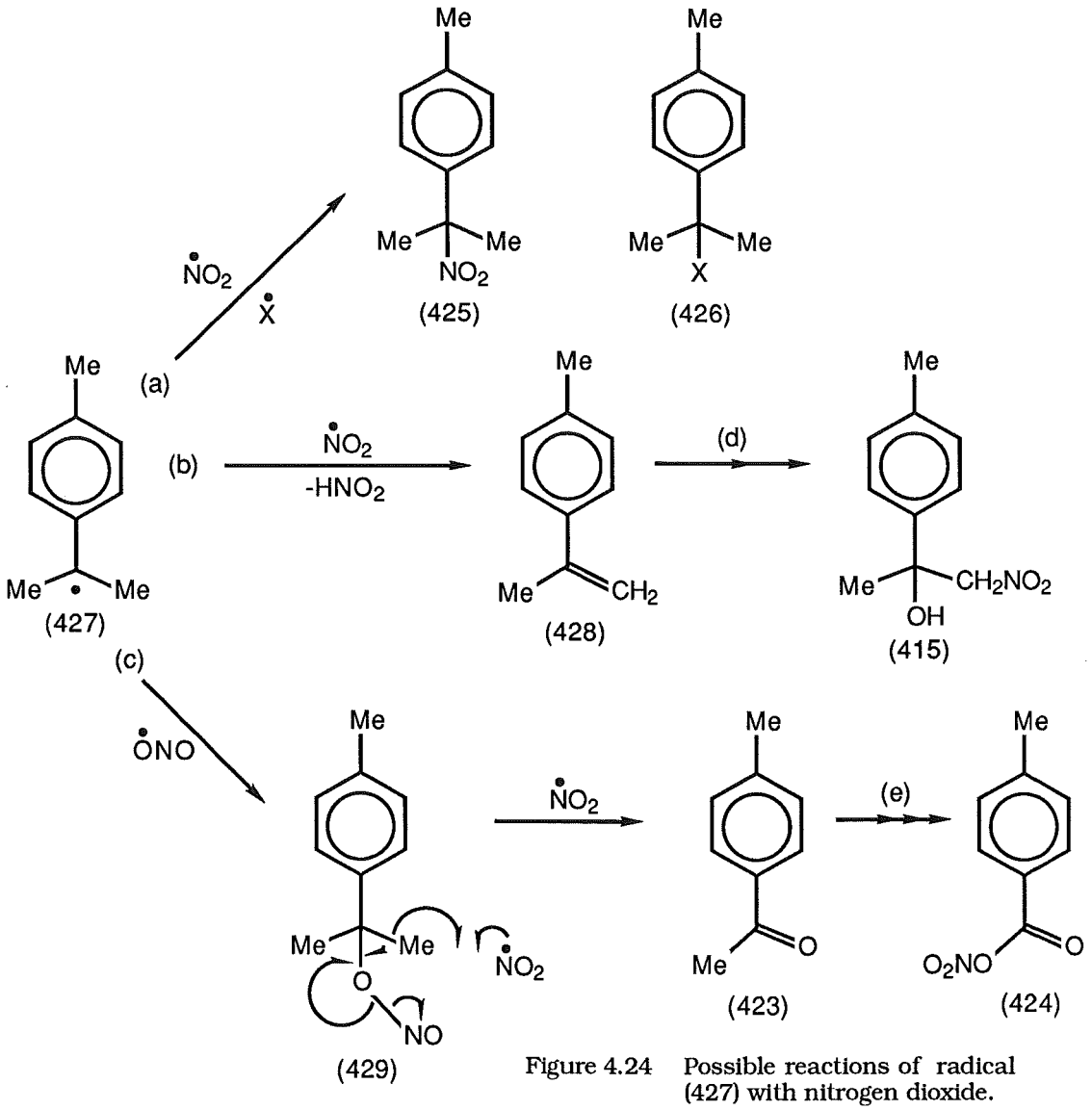


Figure 4.24 Possible reactions of radical (427) with nitrogen dioxide.

resting on the aromatic ring carbons, no products resulting from radical coupling reactions at these aromatic ring carbons are observed in the product mixture. Figure 4.24, above, outlines a number of possible reaction pathways to the formation of the products observed.

Compounds (425) and (426) can arise from simple radical coupling reactions between radical (427), and either a nitrogen dioxide radical, $\dot{N}O_2$, or radical $\dot{X}$ respectively [route (a)]. Furthermore, coupling of radical (427) with a nitrogen dioxide molecule *via* the oxygen atom [route (c)] to give nitrite (429), provides a route to *p*-methylacetophenone (423), the major product of reaction, by a subsequent elimination of a methyl group, possibly as nitromethane.

An alternative fate for radical (427) involves a second hydrogen atom abstraction to yield *iso*-propenyltoluene (428) [Figure 4.24, route (b)]. Subsequent reaction with nitrogen dioxide could then yield compound

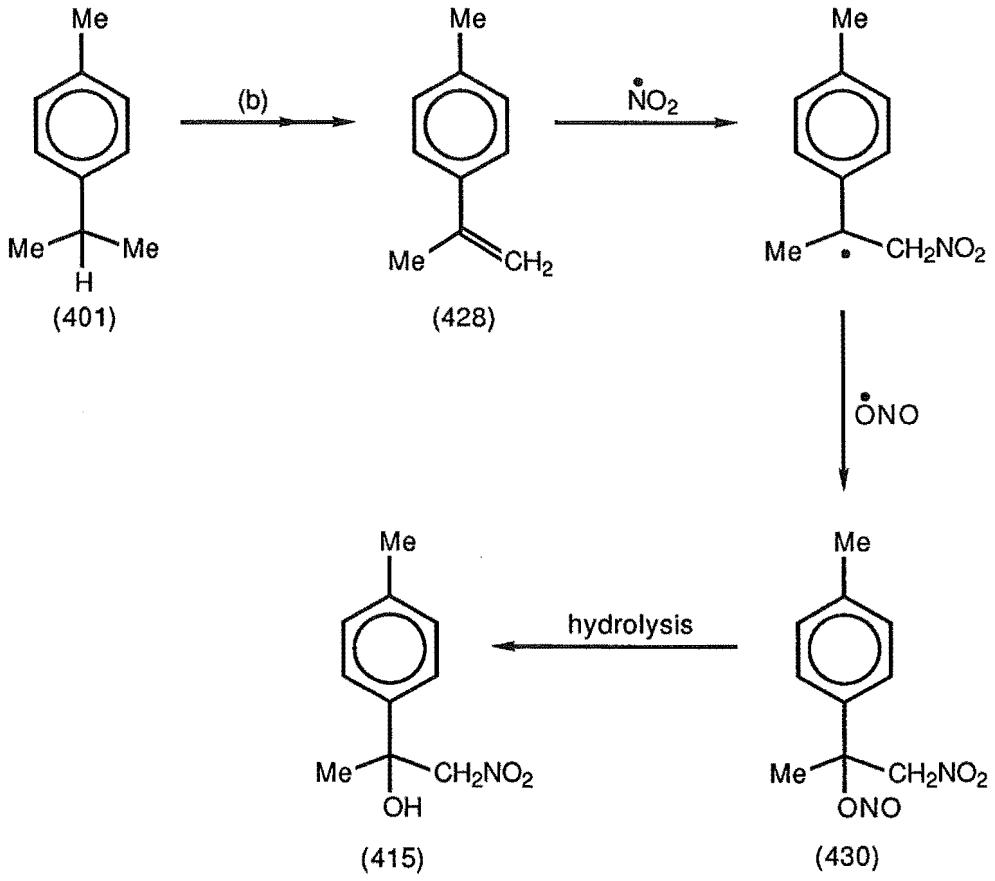


Figure 4.25 Possible reaction pathway to the formation of compound (415). Route (b) is illustrated in full in Figures 4.23 and 4.24 above.

(415) [Figure 4.24, route (d)] by a two step mechanism involving (i) a stepwise addition of two molecules of nitrogen dioxide, the first binding *via* the nitrogen centre and the second binding *via* the oxygen centre, to give the nitrite (430), and (ii) hydrolysis of this nitrite (430) (see Figure 4.25 above). Although no evidence of *iso*-propenyltoluene was found in the product mixture, it seems a likely intermediate in the formation of compound (415).* Furthermore, as is the case for most alkenes, reaction with nitrogen dioxide could be expected to be relatively rapid, and hence the absence of *iso*-propenyltoluene from the product mixture is not surprising.

4.3.2.3 The origin of compound (424) (see Figure 4.24) is unclear, although it may arise as a product of further reaction of *p*-methylacetophenone with nitrogen dioxide [route (e)].

It is worthy of note that, the total mass of the product mixture from the above nitration reaction in dichloromethane (1.24g) is substantially less than the original mass of *p*-cymene committed to the reaction conditions (2.0g). This is undoubtedly a reflection of the unreactivity of *p*-cymene towards nitrogen dioxide under these conditions, as any unreacted *p*-cymene would be readily removed under the high-vacuum workup conditions employed, and account for the drop in mass observed. Indeed, even after 24 hours exposure to an atmosphere of nitrogen dioxide, at least 50% of the *p*-cymene remains unreacted.

4.4 DISCUSSION: THE NITRATION OF DIENES (431), (432) AND (433) IN ACETIC ANHYDRIDE

During the investigation of the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride (see Section 4.2), it was found that when the reaction time was reduced from 24 hours to two hours, (i) the reaction did not proceed to completion (the mass of product obtained suggested only *c.* 30% of the *p*-cymene had reacted), and more significantly (ii) the composition of the product mixture was different to that obtained from the 24 hour reaction, where complete conversion occurred. In particular, a significant

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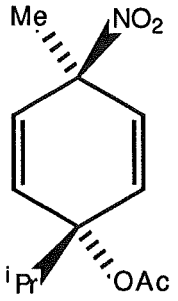
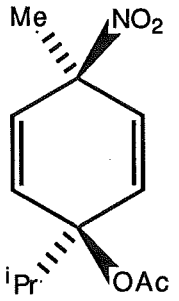
* Ravindranath *et al.* have reported the isolation of iso-propenyltoluene (428) as a product of the free radical bromination of *p*-cymene in carbon tetrachloride (ref. 91).

amount (*c.* 10-15%) of *r*-1-acetato-4-methyl-1-(methylethyl)-*t*-4-nitrocyclohexa-2,5-diene (431) was detected in the ^{1}H n.m.r. spectrum of the crude material. The isomeric *cis* diene (432) may also have been present in lesser amount, but confirmation of its presence was difficult as its ^{1}H n.m.r. resonances occur at similar chemical shifts to those of other compounds in the mixture.



Compound (431)



Compound (432)

The presence of these cyclohexa-2,5-dienes in the reaction mixture after two hours exposure to an atmosphere of nitrogen dioxide, and their subsequent absence from the product mixture when the reaction time is extended to 24 hours, suggests these dienes (i) are susceptible to further attack by nitrogen dioxide, and (ii) may be intermediates in the formation of the final products of reaction. In order to explore these possibilities further, the reactions of the nitro acetoxy dienes (431) and (432) with nitrogen dioxide in acetic anhydride were investigated.

4.4.1 The nitration of diene (431) in acetic anhydride

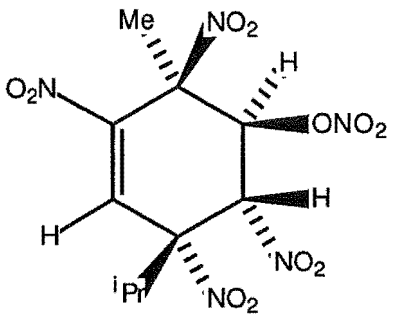
Reaction of *r*-1-acetato-4-methyl-1-(methylethyl)-*t*-4-nitrocyclohexa-2,5-diene (431) with excess nitrogen dioxide in acetic anhydride for 24 hours, gave a crude product which was shown (^{1}H n.m.r.) to be a mixture (*c.* 9:22:6:10:3:1:1:10:9:8:3:6) of 2-nitro-*p*-cymene (403), and the eleven substituted cyclohexenes (410), (411), (412), (413), (416), (417), (418), (419), (420), (421) and (434) respectively. The results of this reaction, and its subsequent workup, reveal several points worthy of note.

(i) The compounds observed as final products of reaction had all been observed as products of the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride solution.

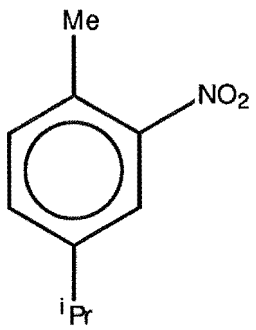
(ii) The relative ratios of the cyclohexenes (410)-(413), (416)-(421) and (434) observed in the crude product mixture are closely similar to the corresponding ratios observed in the *p*-cymene reaction mixture. The major component in both mixtures is the tetranitro nitrate (410) (see diagram below).

(iii) Crystallization of the crude material from the above reaction, from ether/petroleum ether, yielded a white crystalline material, shown (^{1}H n.m.r.) to be compound (410) slightly contaminated with traces of the related compounds (411), (412) and (413) [this parallels the observation made on crystallizing the crude material from the *p*-cymene reaction (see Section 4.2.1.1)]. Subsequent recrystallization of this crystalline mixture, from hexane/dichloromethane, gave a pure, crystalline sample of tetranitro nitrate (410), the ^{1}H n.m.r., ^{13}C n.m.r. and i.r. spectroscopic data for which were identical with the corresponding data for authentic material.

(iv) The percentage yield of 2-nitro-*p*-cymene (403) (9%) from the reaction of the *trans* nitro acetoxy diene (431), is substantially lower than that observed in the *p*-cymene reaction, indicating that most of the 2-nitro-*p*-cymene formed in the reaction of *p*-cymene results from direct nitration of the aromatic ring.



Compound (410)



Compound(403)

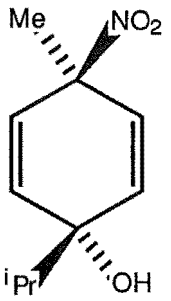
The close similarity of the crude product mixtures obtained from the reaction of (i) the *trans* nitro acetoxy diene (431), and (ii) *p*-cymene, with nitrogen dioxide in acetic anhydride, and the significantly lower yield of aromatic compounds formed in the diene reaction, support the proposed intermediacy of diene (431) in the formation of the cyclohexenes (410)-(413), (416)-(421) and (434) from *p*-cymene. Further discussion regarding possible mechanisms of formation for these cyclohexenes is presented in Section 4.6.

4.4.2 The nitration of diene (432) in acetic anhydride

Reaction of *r*-1-acetato-4-methyl-1-(methylethyl)-*c*-4-nitrocyclohexa-2,5-diene (432) with excess nitrogen dioxide in acetic anhydride for 24 hours, gave a crude product which was shown (^{1}H n.m.r.) to be a mixture (*c.* 12:26:6:9:5:1:1:9:7:6:3:5) of 2-nitro-*p*-cymene (403) and the eleven substituted cyclohexenes (410), (411), (412), (413), (416), (417), (418), (419), (420), (421) and (434) respectively. As was observed for the reaction of the *trans* isomer (431), the products of reaction are identical with the products isolated and identified from the reaction of *p*-cymene. Furthermore, the observation of closely similar ratios between the various cyclohexenes in the reactions of both the *cis* diene (432) and the *trans* diene (431), suggests that the reaction pathways from these dienes to cyclohexene compounds (410)-(413), (416)-(421) and (434), proceed *via* a common intermediate (see Section 4.6 for a more detailed discussion).

4.4.3 Nitration of diene (433) in acetic anhydride

In order to further test the hypothesis that these cyclohexa-2,5-dienes react to give cyclohexenes *via* a common intermediate, a third diene (433) was reacted with nitrogen dioxide under the same conditions. Treatment of *r*-1-hydroxy-4-methyl-1-(methylethyl)-*t*-4-nitrocyclohexa-2,5-diene (433) in acetic anhydride with excess nitrogen dioxide for 24 hours gave a crude product, shown (^{1}H n.m.r.) to be a mixture (*c.* 20:15:4:5:2:1:1:6:5:4:2:3) of compounds (403), (410), (411), (412), (413), (416), (417), (418), (419), (420), (421) and (434) respectively.



Compound (433)

Although the yield of 2-nitro-*p*-cymene (403) is higher, and the yields of the cyclohexenes (410)-(413), (416)-(421) and (434) correspondingly lower, than those observed in the reactions of the nitro acetoxy dienes (431) and (432) with nitrogen dioxide, the ratios between the cyclohexene compounds remain closely similar, supporting the proposal of a common intermediate in the reaction of these cyclohexa-2,5-dienes with nitrogen dioxide to give cyclohexene products.

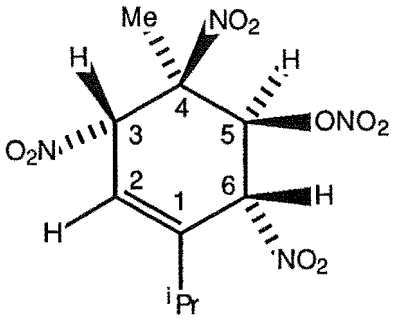
4.5 DISCUSSION: THE NITRATION OF DIENES (431) AND (432) IN DICHLOROMETHANE

On the basis of the results presented in Section 4.4, it seemed likely that the dienes (431) and (432) were reactive intermediates in the nitration of *p*-cymene in acetic anhydride. In order to further explore the nitration reactions of these dienes, their reactions with nitrogen dioxide in dichloromethane solution were investigated. These reactions also offered a further opportunity to explore what, if any, effect the acetic anhydride solvent may have in directing the course of reaction.

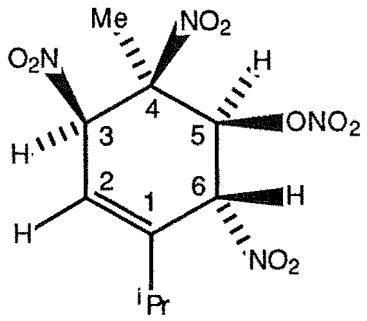
4.5.1 Reaction of *r*-1-acetato-4-methyl-1-(methylethyl)-*t*-4-nitrocyclohexa-2,5-diene (431) with nitrogen dioxide

Reaction of cyclohexa-2,5-diene (431) with excess nitrogen dioxide in dichloromethane solution gave a crude product which was shown (^{1}H n.m.r.) to be a mixture (*c.* 8:8:1:2:2) of two major [compounds (434) and (435)] and three minor [compounds (403), (412) and (438)] components. These components were separated by a combination of crystallization and normal phase h.p.l.c. techniques. The percentage yields quoted below, and in the Experimental Section were estimated from the respective integrals in the ^{1}H n.m.r. spectrum of the crude mixture and do not reflect the amount of pure material isolated.

4.5.1.1 The C3-epimeric trinitro nitrates (434) and (435) were separated from the crude product mixture by crystallization [compound (435)] and normal phase h.p.l.c. [compound (434)] techniques.



Compound (434)



Compound (435)

The structural assignments to the trinitro nitrates (434) and (435) are based on (i) the single crystal X-ray structure analysis performed for compound (434), (ii) the general similarity of the spectroscopic data for the two compounds, (iii) results from selected nuclear Overhauser effect (n.O.e.) experiments, and (iv) the close similarity of the spectroscopic data for the two sets of C3-epimeric pairs, the trinitro nitrates (434) and (435), and the hydroxy dinitro nitrates (418) and (419).

A perspective diagram of 4-methyl-1-(methylethyl)-*t*-5-nitrato-*r*-3,*t*-4,*c*-6-trinitrocyclohexene (434) is presented in Figure 4.26 (corresponding atomic coordinates are given in Section 5.8, Table 15).

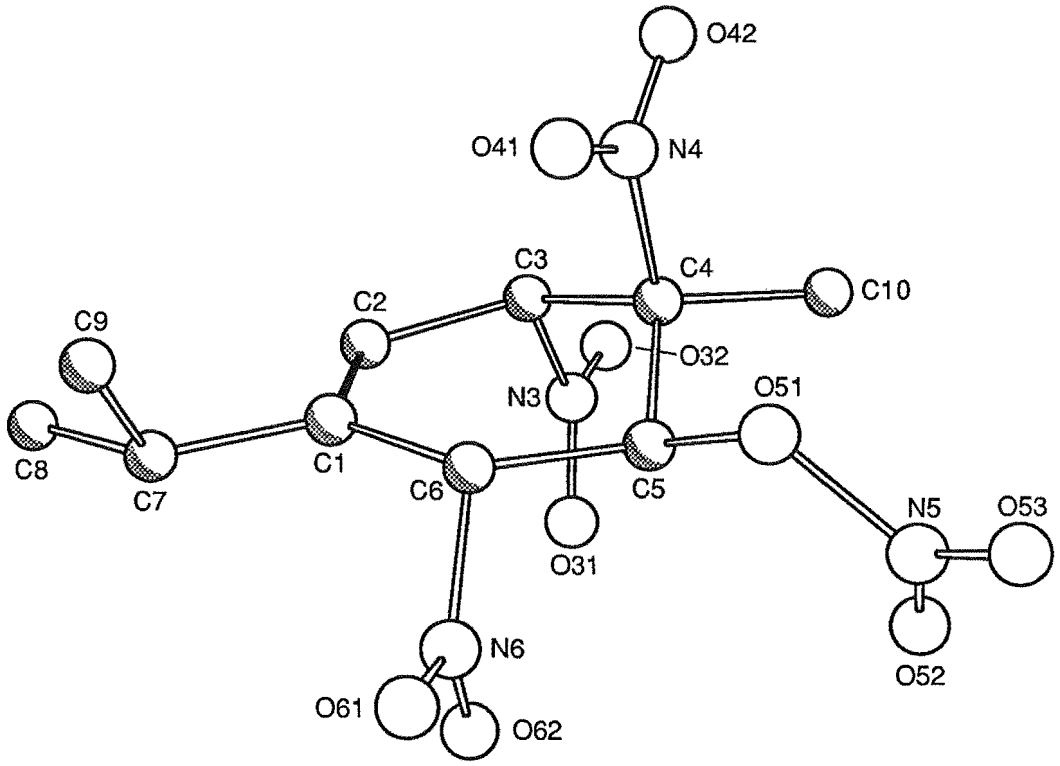


Figure 4.26 Perspective drawing of compound (434). Double bond shown in black.

In the solid state the crystallographic asymmetric unit consists of two chemically equivalent, but crystallographically distinct molecules. Superposition of the two molecules reveals no gross differences of any chemical significance between the two molecules (see Figure 4.27). Both of the independent molecules exist in flattened half chair conformations [torsional angles: molecule 1, C1-C2-C3-C4 -16.5(7)°, C2-C1-C6-C5 -8.0(7)°; molecule 2, C1'-C2'-C3'-C4' 18.4 (8)°, C2'-C1'-C6'-C5' 8.5 (8)°] in which the C3-

substituents are arranged so that H3 lies much closer to the plane of the double bond [torsional angles: molecule 1, H3-C3-C2-H2 45.6(2)°; molecule 2, H3'-C3'-C2'-H2' -45.6 (2)°] than does the C3-nitro group [torsional angles: molecule 1, N3-C3-C2-H2 -74.8(4)°; molecule 2, N3'-C3'-C2'-H2' 73.1(4)°]. The hydrogen atoms H5 and H6, exist in a *trans* relationship and are close to *anti*-coplanar [torsional angles: molecule 1, H5-C5-C6-H6 161.5(1)°; molecule 2, H5'-C5'-C6'-H6' -163.2 (1)°], consistent with the large vicinal coupling constant (*J* 7.5 Hz) observed between these two hydrogens in the solution ^{1}H n.m.r. spectrum.

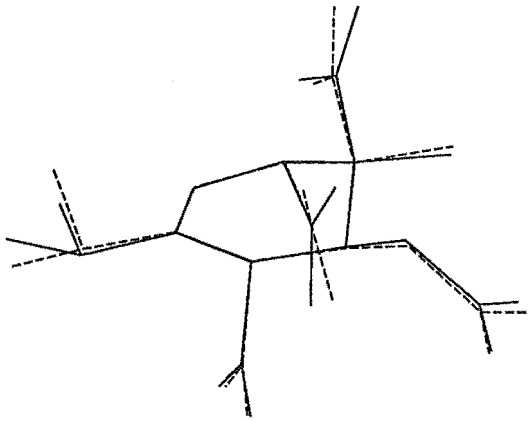
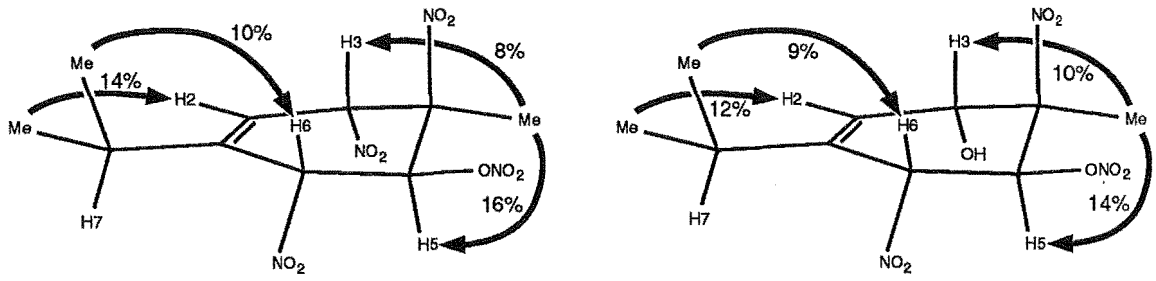


Figure 4.27 Superposition of two molecules of compound (434).

Selected n.O.e. experiments conducted on compound (434) gave results consistent with the structure in the solid state, determined above. Irradiation of the 4-methyl signal resulted in strong enhancements of the signals corresponding to H3 and H5, while separate irradiations of the resonances for the two methyl groups of the *iso*-propyl substituent resulted in enhancement of the signals for H2 and H6 respectively. These n.O.e. correlations are almost identical with those observed for compound (418), which differs from compound (434) only in the nature of the C3-substituent, a hydroxyl group as opposed to the nitro group of compound (434). Furthermore, the coupling patterns found in the ^{1}H n.m.r. spectrum of compound (434) are also closely similar to those observed for compound (418). A summary of the spectroscopic data for the two compounds is presented in Figure 4.28 below.

The close similarity of the ^{1}H n.m.r. and n.O.e. difference spectroscopic data for compounds (434) and (418), when combined with the known structure (single crystal X-ray analysis) for compound (434), provided additional, though belated evidence, to support the structural assignment made for compound (418) (see Section 4.2.3.3), an assignment which, at the time, was uncertain.

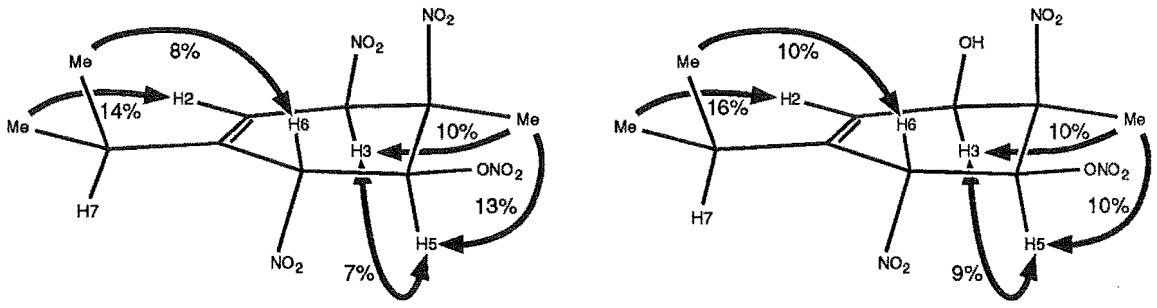


COMPOUND (434)				COMPOUND (418)			
atom	**shift (δ)**		**coupled to:-**	**atom**	**shift (δ)**		**coupled to:-**
H2	6.04	dm	H3 (*J* 5.4 Hz), H6, H7	H2	6.00	dm	H3 (*J* 4.4 Hz), H6, H7
H3	5.82	dm	H2 (*J* 5.4 Hz), H6	H3	4.81	dm	H2 (*J* 4.4 Hz), H6
H5	6.79	d	H6 (*J* 7.5 Hz)	H5	6.37	d	H6 (*J* 5.7 Hz)
H6	5.76	dm	H5 (7.5 Hz), H2, H3, H7	H6	5.62	dm	H5 (5.7 Hz), H2, H3, H7
H7	2.36	m	H2, H6, iPr-methyls	H7	2.25	m	H2, H6, iPr-methyls

Figure 4.28 N.O.e. and n.m.r. spectroscopic data for compounds (434) (left), and (418) (right). Unless listed all coupling constants are in the range: *J* 1-2 Hz.

The other trinitro nitrate (435) was isolated from the crude reaction mixture by crystallization from dichloromethane/hexane, although the crystals thus obtained, were not of sufficient quality to allow a single crystal X-ray structure analysis to be undertaken. Furthermore, the unstable nature of the compound [it rearranges relatively rapidly in solution to a mixture of compounds (418), (419) and (422)], prevented its successful recrystallization. The structural assignment for compound (435) then, is based on spectroscopic evidence. The general (n.m.r., i.r.) spectroscopic data pointed to this compound being a stereoisomer of compound (434), the structure of which has been established by X-ray analysis, above. Furthermore, the presence of a strong, cross-ring n.O.e. correlation between H3 and H5 (see Figure 4.29), which was absent in compound (434), suggests that H3 and H5 in compound (435) must exist in a proximate *cis* relationship. As the X-ray crystal structure analysis reveals that for compound (434) H3 and H5 exist in a *trans* relationship, it seems likely that compound (435) is epimeric with compound (434), either at C3 or at C5. As an alteration of the C5-stereochemistry for compound (434) would result in a substantial decrease in the H4, H5 coupling, through a change in the H4-C4-C5-H5 torsional angle, a decrease which is not observed for compound (435), it seems certain that trinitro nitrate (435) is the C3-epimer of trinitro nitrate (434).

Further support for this structural assignment comes from comparison of the ^{1}H n.m.r. spectroscopic data, and n.O.e. correlation data for compound (434), with similar data for compound (419) (Figure 4.29), the structure for which has been confirmed by single crystal X-ray analysis (see Section 4.2.3.3), and which is related to compound (435) by replacement of the C3-nitro group with a hydroxyl group.



COMPOUND (435)				COMPOUND (419)			
atom	**shift (δ)**		**coupled to:–**	**atom**	**shift (δ)**		**coupled to:–**
H2	6.13	m	H3, H6, H7	H2	5.81	m	H3, H6, H7
H3	5.58	m	H2, H6, H7	H3	4.69	dm	H2, H6, H7, OH(10.6 Hz)
H5	6.10	d	H6 (*J* 8.2 Hz)	H5	6.06	d	H6 (*J* 7.5 Hz)
H6	5.78	dm	H5 (8.2 Hz), H2, H3, H7	H6	5.75	dm	H5 (7.5 Hz), H2, H3, H7
H7	2.30	m	H2, H3, H6, iPr-methyls	H7	2.22	m	H2, H3, H6, iPr-methyls

Figure 4.29 N.O.e. and n.m.r. spectroscopic data for compounds (435) (left), and (419) (right). Unless listed all coupling constants are in the range: *J* 1-2 Hz.

The compounds display closely similar ^{1}H n.m.r. coupling patterns between the five protons H2, H3, H5, H6 and H7, and the only large variations in chemical shift observed between the compounds, at H2 (Δ 0.32 ppm) and H3 (Δ 0.89 ppm) can be readily accounted for in terms of the differing electronic effects exerted by the C3-substituent: a nitro group in compound (435) compared with a hydroxyl group in compound (419). Moreover, the compounds display almost identical n.O.e. correlations, including the cross-ring n.O.e. correlation between the hydrogen atoms H3 and H5.

This structural assignment for compound (435) also allows an explanation for the observation that compound (435) rearranges relatively rapidly in solution, to generate, among other products, compounds (418) and (419). A three step mechanism involving (i) homolysis of the C3-N bond of compound (435) to give a radical pair (436), (ii) recombination of this

radical pair with C3-O bond formation to give a dinitro nitrito nitrate (437), and (iii) hydrolysis of this nitrite (437) to yield the C3-epimeric hydroxy dinitro nitrates (418) and (419), is presented below (Figure 4.30).

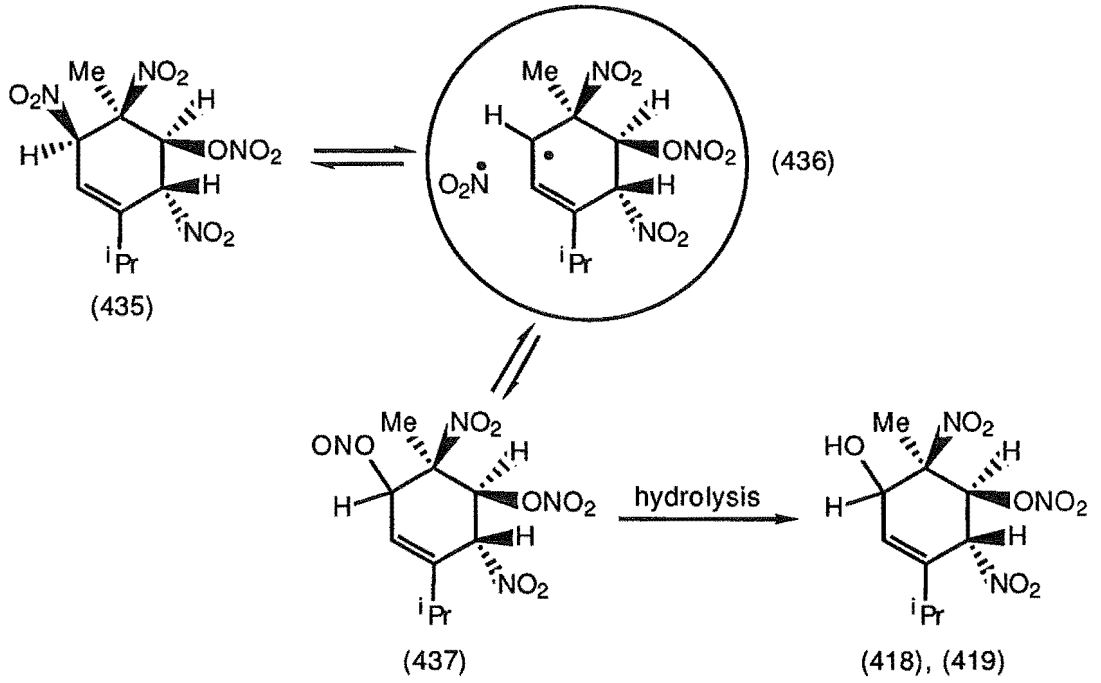
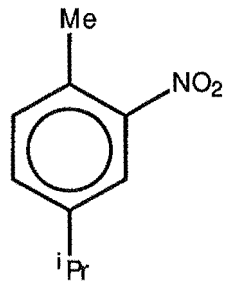
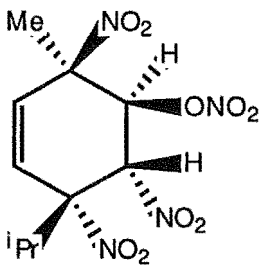


Figure 4.30 Rearrangement of compound (435) to compounds (418) and (419).

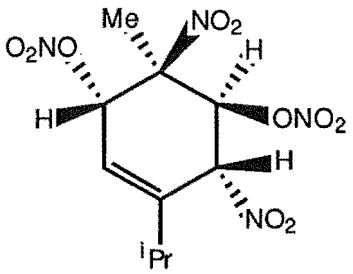
4.5.1.2 Of the three minor products of reaction, both compounds (403) and (412) had been isolated previously, and identified as products of the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride (see Sections 4.2.1 and 4.2.2). These compounds were purified by normal phase h.p.l.c., and their spectroscopic (n.m.r., i.r.) data were identical with the corresponding data from authentic samples.



Compound (403)



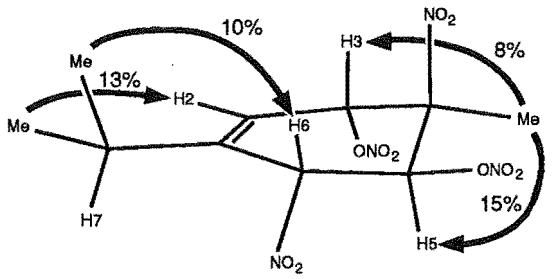
Compound (412)



Compound (438)

The remaining compound was assigned the structure (438). The close similarity of its ^{1}H n.m.r. spectrum to those of compounds (434) and (418) suggested that the stereochemistry was the same for all three compounds.

A summary of the ^{1}H n.m.r., and n.O.e. difference spectroscopic data for compound (438) is presented in Figure 4.31. Comparison of these data with the corresponding data for compounds (418) and (434), presented in Figure 4.28, reveals a close similarity in both the n.O.e. correlations observed and their relative magnitude, and in the proton-proton coupling patterns observed between hydrogens H2, H3, H5, H6 and H7.



COMPOUND (438)

atom	shift (δ)	coupled to:-
H2	5.97 dm	H3 (*J* 5.0 Hz), H6, H7
H3	6.14 dm	H2 (*J* 5.0 Hz), H6
H5	6.24 d	H6 (*J* 6.5 Hz)
H6	5.62 dm	H5 (6.5 Hz), H2, H3, H7
H7	2.30 m	H2, H6, iPr-methyls

Figure 4.31 Selected spectroscopic data for compound (438).

The major evidence for the nitrate group at C3 arises from (i) the presence of strong nitrate absorptions in the i.r. spectrum, and (ii) a comparison of the ^{13}C n.m.r. chemical shift values for C3 and C5 in compounds (418), (434) and (438).

(i) The i.r. spectrum for compound (438) supports the dinitrate structure proposed above. Although two completely distinct sets of the three characteristic nitrate bands are not visible in the i.r. spectrum, there are certainly two absorption bands distinguishable in the 1650-1670 cm^{-1} region (at 1656 and 1666 cm^{-1} respectively) of the spectrum, and the absorption band at 825 cm^{-1} is sufficiently broad to suggest the possible existence of two bands at closely similar wavelength.

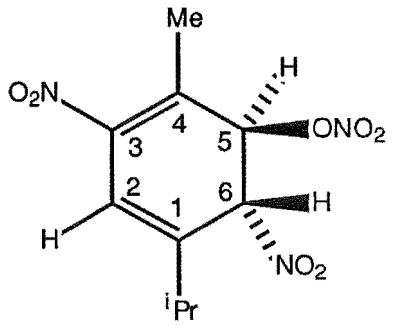
(ii) Comparison of the ^{13}C n.m.r. chemical shifts for C3 and C5 in compounds (418), (434) and (438) provides additional evidence for the C3-

	Compound (418) (C3-hydroxy, C5-nitrate)	**Compound (434)** (C3-nitro, C5-nitrate)	**Compound (438)** (C3-nitrate, C5-nitrate)
C3	68.5 ppm	86.1	76.0
C5	78.3	76.6	77.8

Figure 4.32 Selected ^{13}C n.m.r. chemical shift data for compounds (418), (434) and (438).

nitrate group in compound (438). The ^{13}C n.m.r. chemical shift is strongly dependent on the nature of the attached substituent, and carbons bonded to nitro, hydroxyl, and nitrate groups respectively, occur at markedly different, but characteristic chemical shift positions in the ^{13}C n.m.r. spectrum. As can be seen from Figure 4.32 above, the ^{13}C n.m.r. signal for C3 in compound (438) occurs at δ 76.0 ppm, *c.* 10 ppm upfield of the nitro substituted C3 of compound (434), and *c.* 7.5 ppm downfield of the hydroxy substituted C3 of compound (418). Furthermore, this chemical shift is closely similar to the chemical shift values for the C5 atoms of all three compounds, which are known to be bonded to nitrate groups. It seems likely therefore, that the C3-substituent of compound (438) is also a nitrate group.

4.5.1.3 A further compound (439) was isolated from the h.p.l.c. separation of the products of reaction of diene (431) with nitrogen dioxide in dichloromethane. This compound (439) was not present in the mixture prior to chromatography and is believed to be a decomposition product derived from the genuine reaction products.



Compound (439)

The structural assignment for compound (439), which is itself unstable and rearranges *via* a loss of nitric acid to 2,5-dinitro-*p*-cymene (422), is based on its spectroscopic data, and is supported by the following evidence.

(i) The ^{1}H n.m.r. spectrum is consistent with the proposed structure. First, a COSY[61] experiment reveals that the 4-methyl group hydrogens are weakly coupled with the hydrogen atom H2, consistent with the vinylic methyl group postulated, and second, the coupling constant between H5 and H6 has fallen to *c.* 2.5 Hz, consistent with the decrease in the H5-C5-C6-H6 torsional angle, relative to the cyclohexene compounds, and as expected for the nearly planar cyclohexa-1,3-diene ring of structure (439).

(ii) The ^{13}C n.m.r. spectroscopic data also supports the structural assignment above. First, the resonance for the 4-methyl carbon appears at δ 17.81 ppm,* characteristic of a vinylic methyl group, and *c.* 3 ppm upfield of the other methyl signals. Second, the resonances for C5 and C6 occur at δ 79.15 and 82.24 ppm respectively, consistent with the nitrate and nitro

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* The ^{13}C n.m.r. spectral assignments were confirmed by HETCOR experiments.

substituents in the above structure. Third, the poorly relaxed resonance at δ 147.29 ppm is consistent with the proposed C3, bearing a nitro group.

(iii) The results of selected n.O.e. difference experiments are in accord with the cyclohexadiene structure proposed. Strong correlations are observed between the 4-methyl group hydrogens and H5, and the *iso*-propyl methyl groups and H2 and H6 respectively (see Figure 4.33).

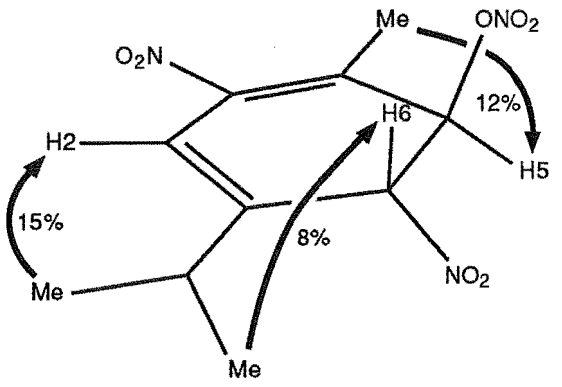


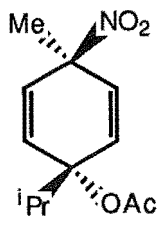
Figure 4.33 Observed n.O.e. enhancements for compound (439).

4.5.2 Reaction of *r*-1-acetato-4-methyl-1-(methylethyl)-*c*-4-nitrocyclohexa-2,5-diene (432) with nitrogen dioxide

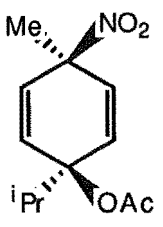
Reaction of the *cis* cyclohexa-2,5-diene (432) with excess nitrogen dioxide in dichloromethane solution gave a crude product of similar composition to that obtained from reaction of the *trans* diene (431), although the yield of 2-nitro-*p*-cymene (403) was higher in the *cis* diene reaction. Inspection of the ^{1}H n.m.r. spectrum revealed a mixture (*c.* 1:1:1) of three major [compounds (434), (435) and (403)] and a large number of minor components. As no new compounds were observed in the crude product, no attempt was made to separate the components of the mixture, the determination of the composition of the mixture being based solely on the compounds' respective ^{1}H n.m.r. spectroscopic data. Similarly, the ratios quoted above were estimated from the respective integrals in the ^{1}H n.m.r. spectrum of the crude material.

4.5.3 Control reactions for compounds (434), (435) and (439)

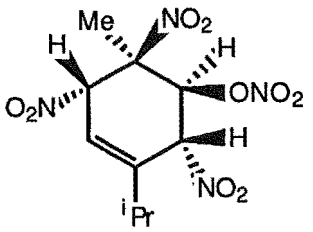
On the basis of the results from the reaction of the cyclohexa-2,5-dienes (431) and (432) with nitrogen dioxide in dichloromethane, it appears that the major products of radical addition to these dienes are the two C3-epimeric trinitro nitrates (434) and (435).



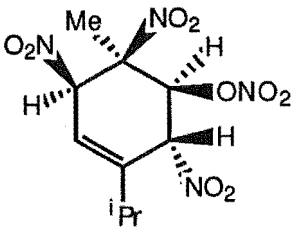
Cpd (431)



Cpd (432)



Compound (434)



Compound (435)

However, only small amounts of compound (434), and no (435), can be identified in the product mixture of the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride solution, even though it has been demonstrated (Section 4.4) that this reaction proceeds *via* the intermediacy of dienes (431) and (432). Consequently, and in order to determine the stability of the trinitro nitrates (434) and (435) under the reaction conditions in acetic anhydride, both compounds were recommitted, separately, to reaction with nitrogen dioxide in acetic anhydride for 24 hours.

4.5.3.1 Reaction of compound (435) with excess nitrogen dioxide in acetic anhydride solution gave a mixture (*c.* 4:1:1:1) of compounds (410), (411), (421) and (420) respectively. Because these compounds had been previously isolated and characterized from the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride, no attempt was made to separate the components of the mixture, and their identification was based solely on their respective ^{1}H n.m.r. spectroscopic data.

4.5.3.2 Exposure of compound (434) in acetic anhydride to excess nitrogen dioxide resulted in only partial reaction, even after 24 hours. Analysis (^{1}H n.m.r.) of the product at this point revealed a mixture (*c.* 30:10:5:2:2:1) of compounds (434) (unreacted starting material), (410), (422), (411), (420) and (421) respectively. Once again, the products were identified on the basis of their respective ^{1}H n.m.r. spectroscopic data, with no attempt being made to separate the individual components of the mixture.

4.5.3.3 The cyclohexa-1,3-diene (439) was also committed to reaction with nitrogen dioxide in acetic anhydride solution, not only because it is a known product of the rearrangement of the trinitro nitrates (434) and (435), but also because it is a likely precursor to the formation of the tetranitro nitrates (410), (421) and (420), by a stepwise addition of nitrogen dioxide to the diene system (Figure 4.34).

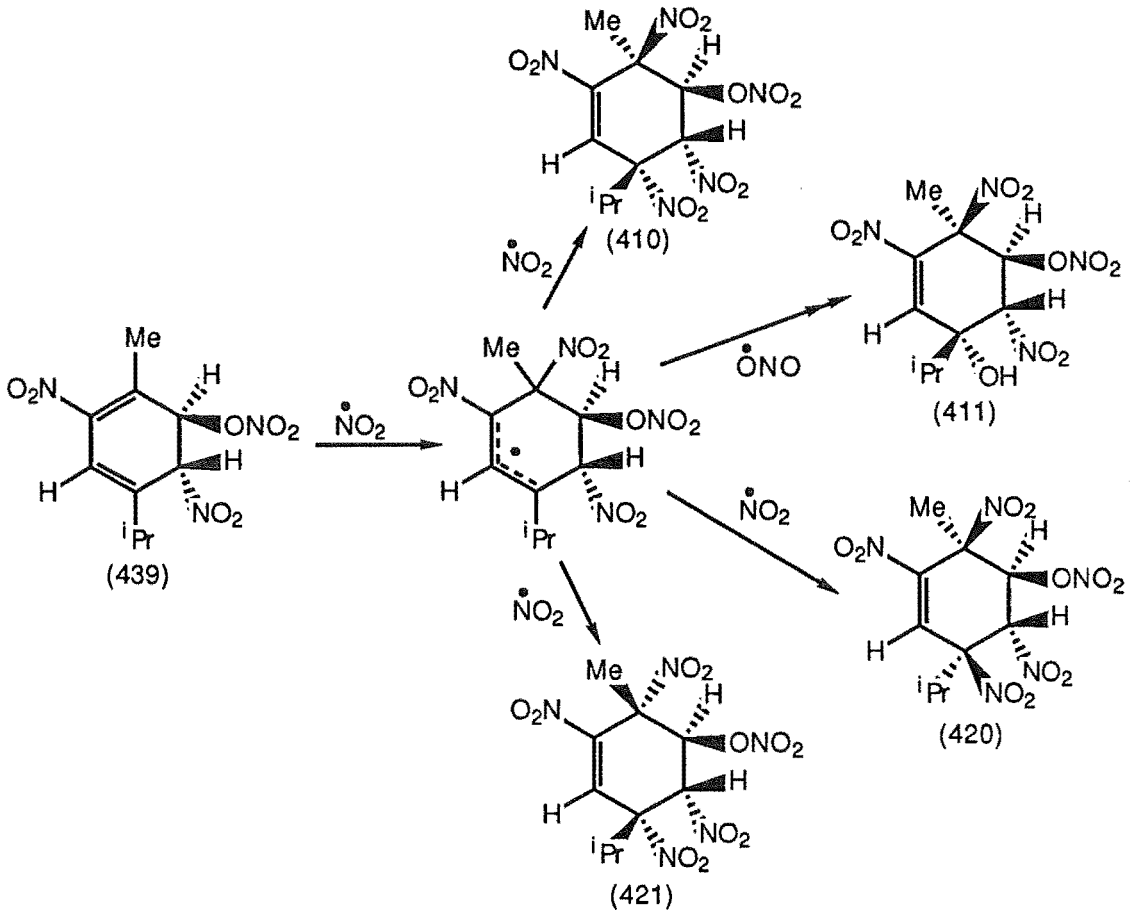


Figure 4.34 Stepwise addition of nitrogen dioxide to cyclohexa-1,3-diene (439).

Reaction of cyclohexa-1,3-diene (439) with excess nitrogen dioxide in acetic anhydride solution gave a mixture (*c.* 9:2:4:3) of the cyclohexenes (410), (411), (421) and (420) respectively. These compounds were identified on the basis of their respective ^{1}H n.m.r. spectroscopic data.

4.6 DISCUSSION: REACTION PATHWAYS IN THE NITRATION OF *PARA*-CYMENE

The reaction of *p*-cymene with excess nitrogen dioxide in acetic anhydride solution has been shown (Section 4.2) to yield a multitude of substituted cyclohexenes as products of reaction. On the basis of the observations and evidence discussed in Sections 4.2-4.5, a reaction scheme to account for the formation of these compounds is presented in Figure 4.35.

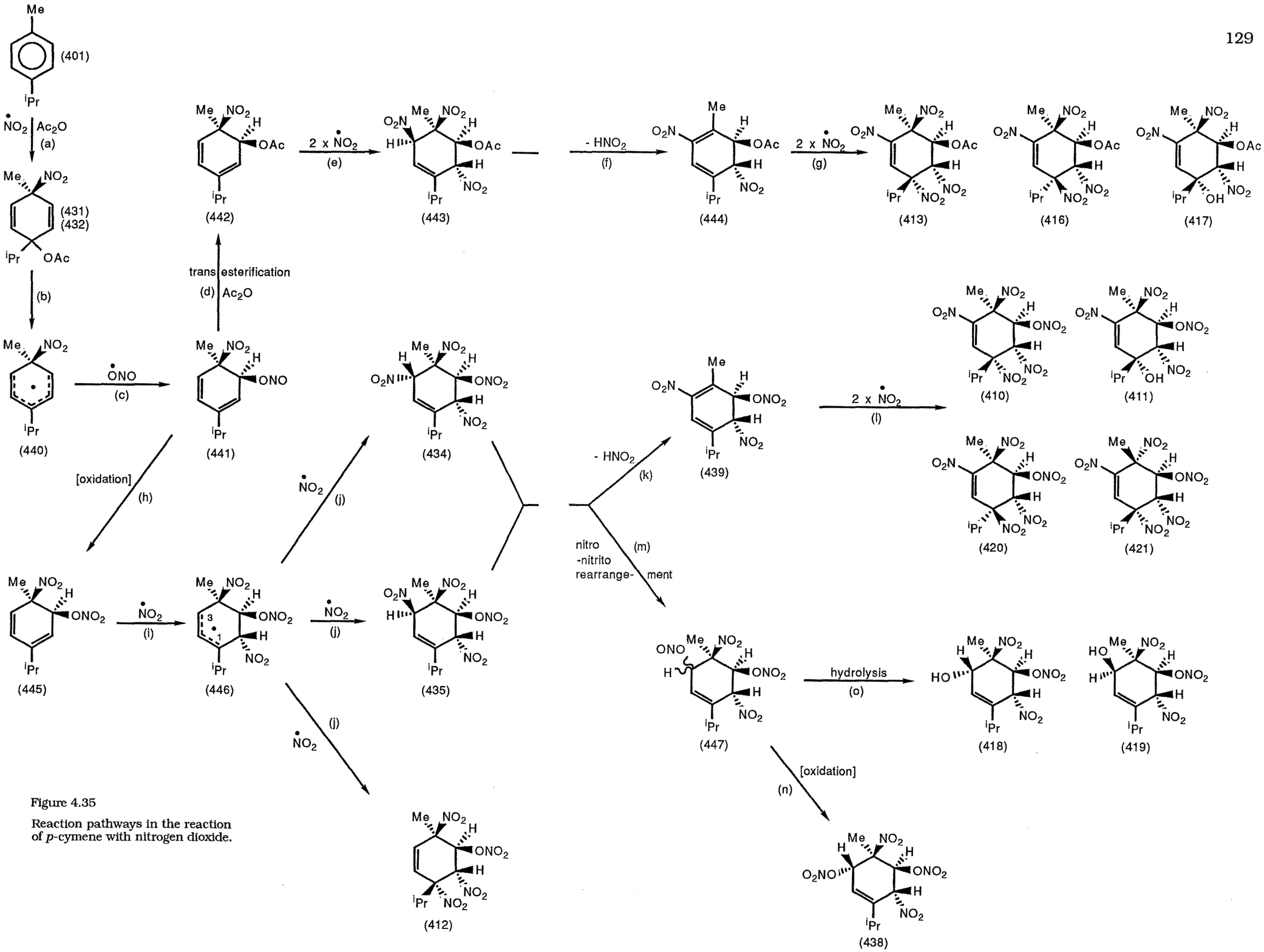


Figure 4.35

Reaction pathways in the reaction of *p*-cymene with nitrogen dioxide.

In the following discussion aspects of the above reaction scheme (Figure 4.35) will be highlighted, and where applicable, evidence supporting the reaction processes outlined in the scheme will be discussed.

4.6.1 Cyclohexa-2,5-diene formation

The intermediacy of the cyclohexa-2,5-dienes (431) and (432) [route (a), Figure 4.35] in the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride solution is fairly certain. The *trans* isomer (431) is observed (^{1}H n.m.r.) in the reaction mixture after 2 hours exposure to nitrogen dioxide, but is not observed in the final product mixture, implying that once formed, it undergoes further reaction with nitrogen dioxide. Furthermore, reaction of a pure sample of either diene (431) or (432) with nitrogen dioxide in acetic anhydride, is known to yield a very similar product mixture to that formed in the *p*-cymene reaction (see Section 4.4).

The mode of formation of these cyclohexa-2,5-dienes (431) and (432) from *p*-cymene however, remains uncertain. The fact that nitration of *p*-cymene in dichloromethane does not yield these dienes, suggests that the acetic anhydride solvent is actively involved in the diene formation. Indeed, comparison of the nitrogen dioxide nitration of *p*-cymene in acetic anhydride, with the nitric acid nitration of *p*-cymene in acetic anhydride allows further comment to be made.

Reaction of *p*-cymene with nitric acid in acetic anhydride has been shown to yield cyclohexa-2,5-dienes (431) and (432) as the major products of reaction.[86] Furthermore, it has long been known that mixtures of nitric acid and acetic anhydride react rapidly to form acetyl nitrate and acetic acid, and that in excess acetic anhydride this reaction proceeds to completion (Figure 4.36).[92]

$$Ac_2O + HNO_3 \rightleftharpoons AcONO_2 + AcOH$$

Figure 4.36 Formation of acetyl nitrate from acetic anhydride.

Hence, it is actually the reaction of *p*-cymene with acetyl nitrate which forms the cyclohexa-2,5-dienes, although the nature of the actual nitrating species involved is uncertain: the cationic nitronium ion (NO_2^+), and

protonated acetyl nitrate ($MeCO_2NO_2H^+$) are considered the most likely electrophiles.[93]

On the basis of the information above, it is possible that the nitrogen dioxide nitration of *p*-cymene in acetic anhydride, like the nitric acid nitration, proceeds *via* the formation of acetyl nitrate, $AcONO_2$, which subsequently generates the active nitrating species required to form the cyclohexa-2,5-dienes (431) and (432).

4.6.2 Generation of cyclohexenes (412), (431) and (435)

The trinitro nitrato cyclohexenes (412), (434) and (435) are isolated as final products from the reaction of cyclohexa-2,5-dienes (431) and (432) with nitrogen dioxide in dichloromethane (see Section 4.5) solution. The formation of compounds (412), (434) and (435) from the dienes (431) and (432) is best accounted for in terms of the reaction processes (b), (c), (h), (i) and (j) presented in Figure 4.35.

4.6.2.1 The observation that both the *trans* and *cis* isomers of the nitro acetoxy cyclohexa-2,5-dienes, compounds (431) and (432) respectively, yield the same products, with the same stereochemistry, implies that the configuration of the acetate group in the reactant diene is irrelevant. Consequently, the reactions to generate cyclohexenes (412), (434) and (435) must proceed *via* a common intermediate, postulated as structure (440) [route (b), Figure 4.35]. This resonance stabilized radical is seen as forming *via* removal of the acetate group by a nitrogen dioxide radical (Figure 4.37).

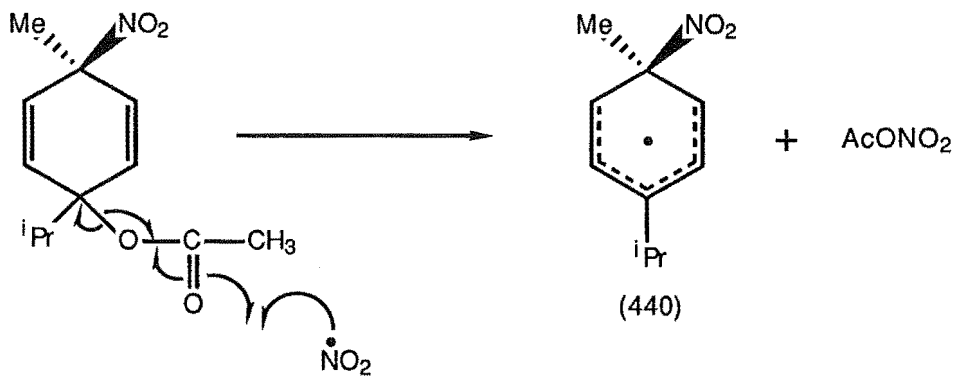


Figure 4.37 Reaction of cyclohexa-2,5-diene with nitrogen dioxide.

4.6.2.2 The further reaction of the delocalized radical (440) with nitrogen dioxide is interesting in that it occurs with a high degree of stereospecificity. The final products from the nitration of dienes (431) and (432) in dichloromethane [compounds (412), (434) and (435)] all have structures with a *cis* relationship between the C4-nitro group and the C5-nitrate group, a fact which demands that the radical coupling between radical (440) and nitrogen dioxide similarly occurs to yield only the *cis* 4-nitro 5-nitrito cyclohexadiene (441) [route (c), Figure 4.35].

On the basis of this strong specificity for attack at C5 of radical (440) *cis* to the C4-nitro group, it appears likely that some pre-association occurs between the C4-nitro group of radical (440) and the approaching nitrogen dioxide molecule, possibly involving a dipole-dipole interaction between the electronegative oxygen atom of the C4-nitro group and the electrophilic nitrogen atom of the approaching nitrogen dioxide radical (see Figure 4.38).

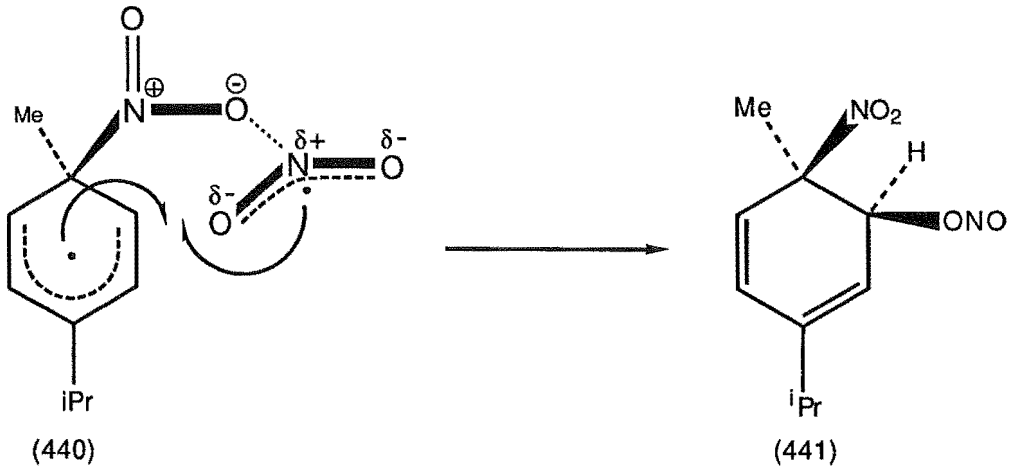


Figure 4.38 Pre-association mechanism for the formation of diene (441).

This pre-association mechanism would constrain the attacking nitrogen dioxide radical, in a position where subsequent radical coupling would (i) generate a product with a *cis* relationship between the C5-substituent and the C4-nitro group, and (ii) occur exclusively with C5-O bond formation. Such a radical coupling then, is consistent with the observation that the three major final products of reaction in dichloromethane, cyclohexenes (412), (434) and (435), all have C5-O bonded, nitrate substituents *cis* to the C4-nitro group.

4.6.2.3 The oxidation of the C5-nitrite substituent to a nitrate group by dinitrogen tetroxide and/or dinitrogen tetroxide/oxygen mixtures is a documented reaction,[37,94] although the nature of the oxidizing agent

remains uncertain: the most likely oxidizing agent is N_2O_5 (or $^{\bullet}NO_3$), possibly produced *in situ* by reaction of nitrogen tetroxide with oxygen. It should be noted that, although the oxidation step has been included at this point in the reaction scheme for the sake of clarity, it is feasible that this oxidation could occur at any point along the reaction pathway leading to the final products.

4.6.2.4 The reactions of cyclohexa-1,3-dienes with nitrogen dioxide are known to occur rapidly,[49] and hence the addition of nitrogen dioxide to cyclohexadiene (445) to form delocalized radical (446) [route (i), Figure 4.35] should occur readily. Interestingly, and on the basis of the stereochemistry observed in the products, nitrogen dioxide attack at C6 of diene (445) occurs exclusively *trans* to the C5-nitrate group. This stereospecificity is probably the result of steric factors. First, the C4-nitro and C5-nitrate groups shield to some extent one side of the diene system, hindering the approach of a nitrogen dioxide molecule from this side of the ring, and second, attack at C6 from this more hindered side, involving nitrogen dioxide attack *cis* to the C5-nitrate group, would yield a product radical (446) in which strong steric interactions exist between the C4- and C6-nitro groups. As a result of these factors, the preferred mode of reaction involves a radical attack at C6 *trans* to the C5-nitrate group.

Delocalized radical (446) can react further with nitrogen dioxide by a radical coupling reaction at either C1 or C3. From the percentage yields observed in the product mixture, it is apparent that coupling at C3 is preferred, presumably because the *iso*-propyl group at C1 offers considerable hindrance to an approaching nitrogen dioxide molecule, thus disfavouring coupling at the C1 position. The major products of radical coupling then, are the C3-epimeric cyclohexenes (434) and (435), arising from nitrogen dioxide attack at C3 of radical (446), either *trans* or *cis* to the C4-nitro group respectively. Compound (412), arising from radical coupling at C1, is formed as a minor product of reaction.

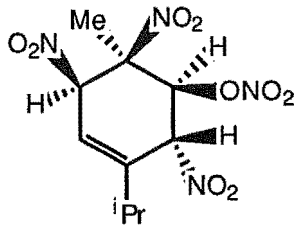
4.6.3 Further reaction of cyclohexenes (434) and (435)

Despite the fact that the trinitro nitrato cyclohexenes (434) and (435) are inert to further reaction with nitrogen dioxide in dichloromethane solution, separate reactions of pure samples of these two cyclohexenes with nitrogen

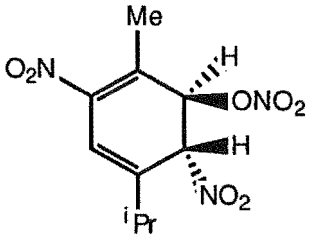
dioxide in acetic anhydride solution, reveal that under these conditions further reaction does occur (see Section 4.5.3). Furthermore, the products of these reactions, compounds (410), (411), (418), (419), (420) and (421), are all observed as final products from the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride.

Although the cyclohexenes (434) and (435) differ only in the relative stereochemistry at C3, their respective chemical properties are quite different. Cyclohexene (435) undergoes rearrangement in solution more readily, and the product of this rearrangement is susceptible to further reaction with nitrogen dioxide.

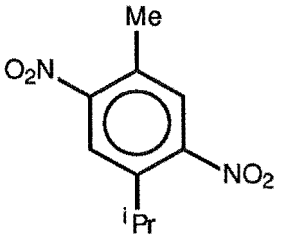
4.6.3.1 Although cyclohexene (435) is relatively stable in dichloromethane solution (as evidenced by the fact that it is isolated as a major product, from the 24 hour reaction of cyclohexadiene (431) with nitrogen dioxide), in deuteriochloroform solution it undergoes rearrangement, forming initially cyclohexa-1,3-diene (439), and ultimately 2,5-dinitro-*p*-cymene (422).



Compound (435)

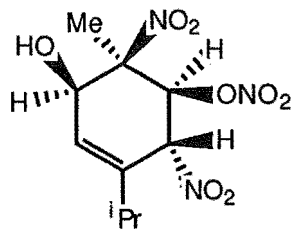


Compound (439)



Compound (422)

Inspection of the relative orientations of the H3 atom and the C4-nitro group in the structure of compound (435), allows an explanation for this facile loss of nitrous acid to form diene (439) [route (k), Figure 4.35].



Compound (419)

The C3-H3 bond should be close to *anti*-coplanar with the C4-N4 bond in compound (435), because H3 and the C4-nitro group occupy *pseudo*-axial and axial positions respectively in the structure. Indeed, confirmation of the *anti*-coplanar relationship between these two substituents can be obtained by inspection of the torsional

angles from the single crystal X-ray analysis performed for the structurally related cyclohexene (419). On the assumption that the conformations of the stereochemically equivalent cyclohexenes (435) and (419) are similar, the H3-C3-C4-N4 torsional angle in compound (435) can be well approximated by the corresponding torsional angle for compound (419), which is calculated from the X-ray analysis to be 170.8(2)°.

The nearly *anti*-coplanar relationship between H3 and the C4-nitro group in cyclohexene (435), means an E2-type elimination of nitrous acid across the C3-C4 bond will occur readily (Figure 4.39), yielding the cyclohexa-1,3-diene (439). The presence of significant quantities of acid in deuteriochloroform solution is presumably why the rearrangement is observed in this solvent, but is not observed in dichloromethane solution.

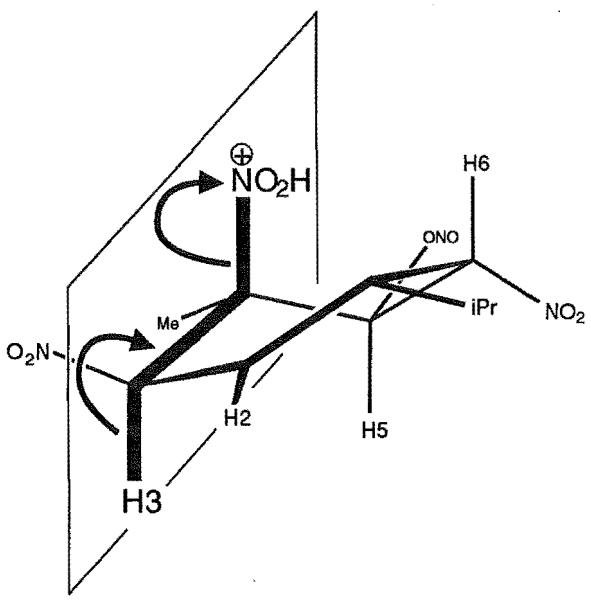


Figure 4.39 E2 elimination of nitrous acid from compound (435).

Once formed, cyclohexa-1,3-diene (439) will react rapidly in the presence of nitrogen dioxide [route (l), Figure 4.35], *via* a stepwise addition of nitrogen dioxide to the diene system (Figure 4.40). The three diastereoisomeric tetranitro nitrates (410), (420) and (421), and the hydroxy trinitro nitrate (411) are formed as the only products of reaction. Noticeably, and confirming the intermediacy of diene (439) in the further reactions of cyclohexene (435) with nitrogen dioxide, cyclohexene (435) reacts with nitrogen dioxide in acetic anhydride to give the same four products, in similar ratios, as the sole products of reaction.

From the isolation of the hydroxy trinitro nitrate (411) as a minor reaction product it is clear that radical coupling between delocalized radical (448) and the nitrogen dioxide occurs not only to give C1-nitro compounds, but also *via* the oxygen centre of nitrogen dioxide to generate a C1-nitrite (449). The nitrite compound thus formed, will convert to the hydroxy trinitro nitrate (411) by hydrolysis of the nitrite group (see Figure 4.41).

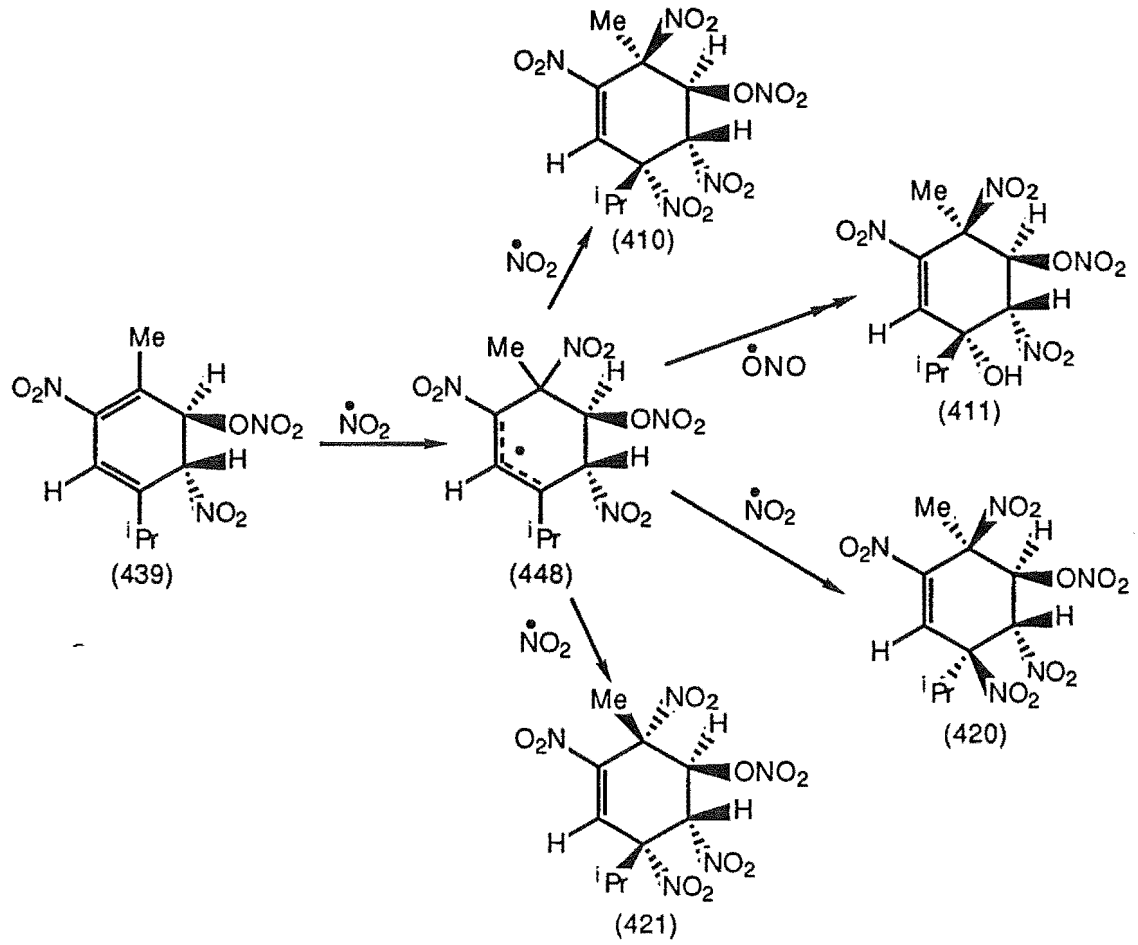


Figure 4.40 Nitrogen dioxide addition to cyclohexa-1,3-diene (439).

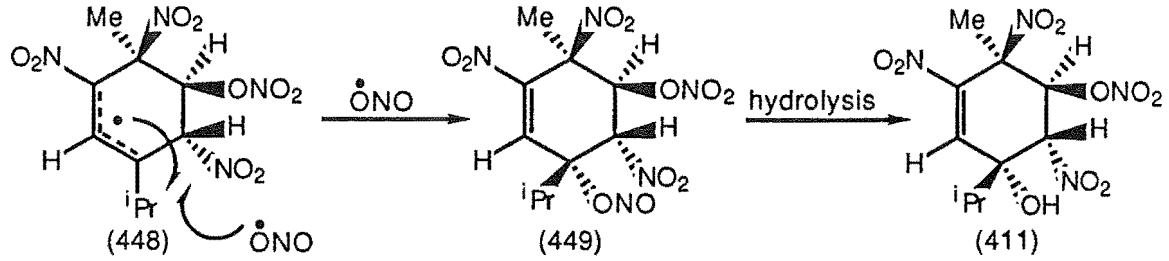


Figure 4.41 Reaction of delocalized radical (448) to form hydroxy trinitro nitrate (411).

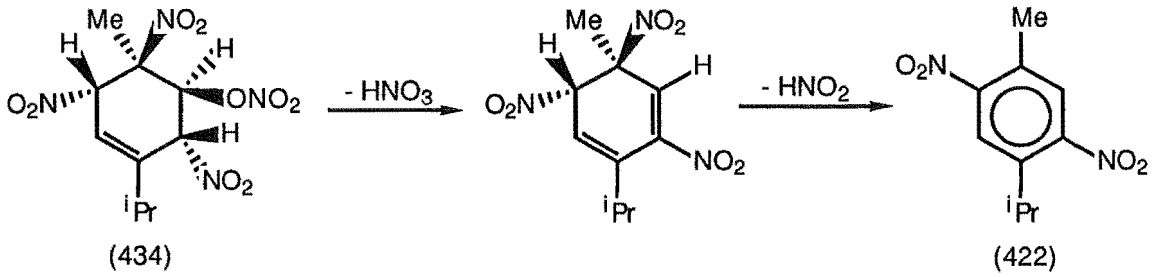
From the relative yields of the hydroxy trinitro nitrate (411) (4%),* generated by radical coupling with C-O bond formation, and the stereochemically equivalent tetranitro nitrate (410) (16%), arising from radical coupling with C-N bond formation, it is apparent that coupling between radical (448) and nitrogen dioxide occurs preferentially with C-N bond formation, and that coupling with C-O bond formation represents only

* The percentages refer to approximate yields in the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride solution.

a minor pathway (ratio C-N:C-O *c.* 4:1). Consequently, the failure to isolate the hydroxy trinitro nitrato stereochemical equivalents of tetranitro nitrates (420) and (421) from the reaction mixture is hardly surprising, as although they are undoubtedly present, they will represent such a small percentage of the total mixture that their isolation would be unlikely.

On the basis of the arguments presented above, it is clear that it is the rearrangement to diene (439) which accounts for the apparent reactivity of cyclohexene (435) towards nitrogen dioxide in certain solvents (*e.g.* acetic anhydride) as it is not the cyclohexene itself, but the product of its rearrangement, cyclohexa-1,3-diene (439), which undergoes further reaction with nitrogen dioxide. The reaction solvent then, is the determining factor in the reaction of compound (435) with nitrogen dioxide: in those solvents which facilitate the E2 elimination of nitrous acid to form diene (439) (see Figure 4.39), reaction to tetranitro nitrates (410), (420) and (421) and hydroxy trinitro nitrate (411) will occur readily, whereas in solvents where the E2 elimination is unfavourable (*e.g.* dichloromethane), unreacted compound (435) is isolated as the major component of the product mixture.

4.6.3.2 In contrast to its C3-epimer, cyclohexene (434) is relatively inert to further reaction with nitrogen dioxide, even in acetic anhydride solution. Certainly, the decreased efficiency of the elimination to yield diene (439) [with respect to compound (435)] is not surprising, as the structural geometry no longer favours an E2 elimination across the C3-C4 bond (H3-C3-C4-N4 torsional angle: molecule 1, 40.1(3)°; molecule 2, -43.7(4)°). The decreased efficiency of the elimination reaction to yield diene (439), means other rearrangement mechanisms become more important. An alternative elimination mechanism involving (i) an elimination of nitric acid across the C5-C6 bond, and (ii) a subsequent loss of nitrous acid to yield 2,5-dinitro-*p*-cymene is presented in Figure 4.42.



(434) (422)

Figure 4.42 Rearrangement of compound (434) to 2,5-dinitro-*p*-cymene (422).

Despite the operation of both the above elimination mechanisms (Figures 4.39 and 4.42), compound (434) remains relatively inert to further reaction with nitrogen dioxide in acetic anhydride solution: after 24 hours exposure to an atmosphere of nitrogen dioxide only *c.* 40% of compound (434) has undergone reaction, yielding limited amounts of compounds (410), (411), (420), (421) and (422), by the rearrangement mechanisms discussed above.

4.6.3.3 A further reaction possibility for cyclohexenes (434) and (435) involves a nitro-nitrito rearrangement of the C3-nitro group to give the corresponding dinitro nitrito nitrate (447) [route (m), Figure 4.35]. It should be noted that although the dinitro nitrito nitrate (447) is included in Figure 4.35 only as a product of the nitro-nitrito rearrangement of compounds (434) and (435), it may also be formed directly from delocalized radical (446), by a radical coupling reaction with a nitrogen dioxide radical *via* one of the oxygen atoms.

Once formed, the nitrito nitrate (447) can undergo subsequent reaction in two ways: (i) by hydrolysis of the nitrite group [route (o), Figure 4.35] to a hydroxyl group, yielding the C3-epimeric hydroxy dinitro nitrato cyclohexenes (418) and (419), and (ii) by oxidation of the C3-nitrite group [route (n), Figure 4.35] to a nitrate group, yielding the dinitro dinitrato cyclohexene (438).

4.6.4 The origin of acetate compounds (413), (416) and (417)

The acetates (413), (416) and (417) were isolated as minor products from the reactions of either *p*-cymene or cyclohexa-2,5-dienes (431) and (432) with nitrogen dioxide in acetic anhydride solution, but were not formed in either of the corresponding reactions in dichloromethane solution. On the basis of these observations, it seems certain that the acetic anhydride solvent is the origin of the acetate groups found in the structures of compounds (413), (416) and (417).

A likely mechanism for the formation of these acetate groups is presented in Figure 4.43 below, and involves a transesterification of the nitrite group of diene (441) [route (d), Figure 4.35] to yield the corresponding acetoxy diene (442). It should be noted that, because this transesterification is accomplished without breaking the C-O bond of nitrite (441), the process

occurs with retention of configuration and the stereochemistry of the product diene (442) is identical with that of the reactant diene (441).

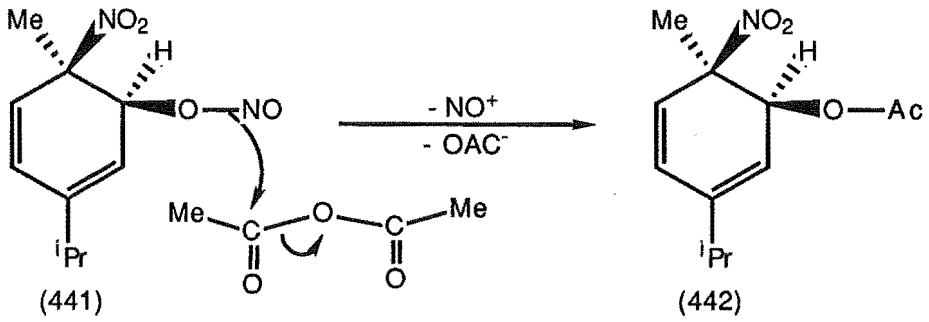


Figure 4.43 Transesterification of the nitrite group of diene (441).

Because of the close similarity between the structures of the nitrato diene (445) and the stereochemically equivalent acetoxy diene (442), the subsequent reactions of acetoxy diene (442) with nitrogen dioxide are envisaged as occurring *via* similar reaction processes to those established for the nitrato diene (445); *i.e.* a three step mechanism involving (i) a stepwise addition of two molecules of nitrogen dioxide, yielding the trinitro acetate (443) [route (e), Figure 4.35], (ii) elimination of nitrous acid across the C3-C4 bond of compound (443) to form the cyclohexa-1,3-diene (444) [route (f), Figure 4.35], and (iii) subsequent stepwise addition of nitrogen dioxide to this diene system, generating the cyclohexenes (413), (416) and (417).

This proposal for similar mechanisms for the generation of the acetates (413), (416) and (417), and the nitrates (410), (411), (420) and (421) is supported by the fact that the relative yields of acetates (413), (416) and (417) (*c.* 4:1:1) closely parallel the relative yields of the stereochemically equivalent nitrates, compounds (410), (420) and (411) (*c.* 4:1:1).

4.6.5 Formation of aromatic nitro compounds (403) and (405)

The aromatic nitro compounds (403) and (405) are significant products in the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride solution, accounting for 24% and 8% of the crude product mixture respectively. The formation of these products can be accounted for in terms of conventional aromatic nitration mechanisms, involving radical Wheland intermediates.

Figure 4.44 illustrates the reaction pathways to the formation of compounds (403) and (405).

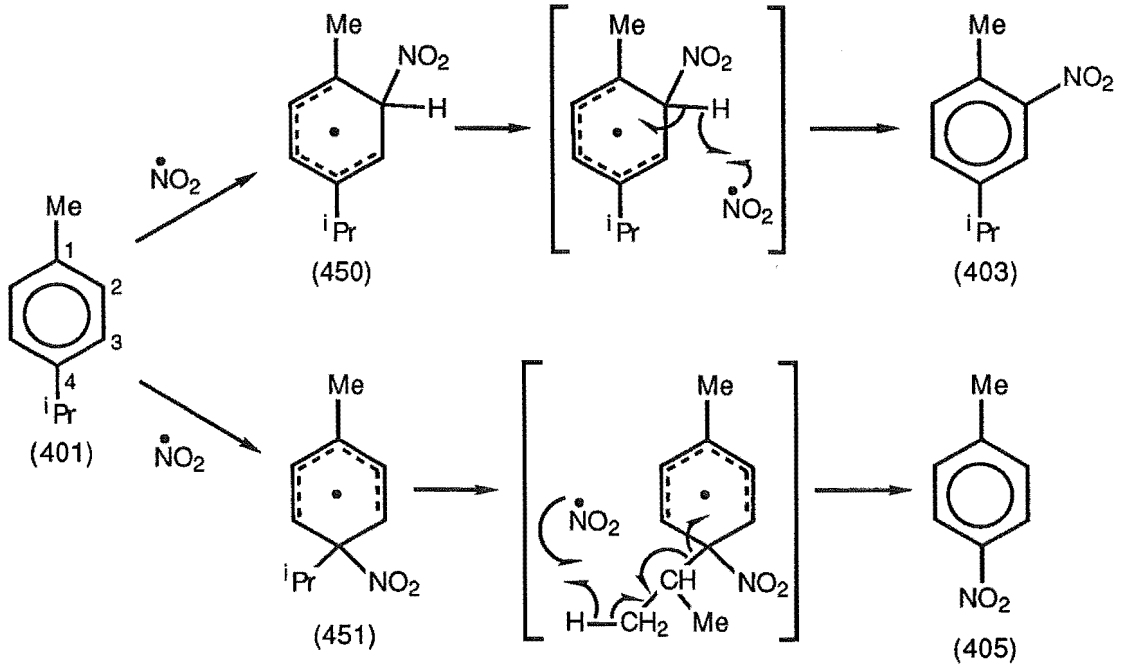


Figure 4.44 Reaction pathways to the formation of compounds (403) and (405).

Attack at C2 by a nitrogen dioxide molecule will generate the radical Wheland intermediate (450), which by loss of a hydrogen atom yields 2-nitro-*p*-cymene (403). In contrast, *p*-nitrotoluene (405) arises from initial nitrogen dioxide attack at C4, *ipso* to the *iso*-propyl group, generating Wheland intermediate (451). Unlike delocalized radical (450), hydrogen atom loss is not a reaction possibility for Wheland intermediate (451) and so subsequent reaction occurs *via* loss of the *iso*-propyl group, forming *p*-nitrotoluene (405).

CHAPTER FIVE

EXPERIMENTAL RELATING TO PART TWO

A discussion of the general experimental methods used in the course of this research, including descriptions of the chemical materials and the various types of instrumentation used, and a summary of the method used for synthesis of nitrogen dioxide, is presented at the beginning of Chapter three, in Section 3.1.

5.1 REACTION OF *P*-CYMENE WITH NO_2 IN ACETIC ANHYDRIDE

A solution of *p*-cymene (2g) in acetic anhydride (2ml) was de-oxygenated by a stream of pure nitrogen. Nitrogen dioxide was bubbled through the solution at 0-5° for 30 seconds, and the resulting solution stirred, under an atmosphere of nitrogen dioxide, for 24 hours at room temperature. Following reaction, the excess nitrogen dioxide was removed in a stream of nitrogen, and the solvent removed under reduced pressure. The residue was an orange/red oil (3.68g), which was shown (^{1}H n.m.r.) to be a very complex mixture.

5.1.1 Isolation of compounds (410), (411), (412), (413) and (422)

Crystallization of the crude product from ether/petroleum ether at 2° gave a yield of white crystals (337mg), shown by ^{1}H n.m.r. spectroscopy to be a mixture (*c.* 20:1:2:2) of four compounds (410), (411), (412) and (413). The crystals were washed with ether (see below for material isolated from washings), and then recrystallized from dichloromethane/petroleum ether to give a single, pure compound (410).

6-methyl-3-(methylethyl)-t-5-nitrato-1,r-3,c-4,t-6-tetranitrocyclohexene **(410)**[87] (16%)* m.p. 127.5-129° (lit.[81] 127-129°) (structure determination by single crystal X-ray analysis, see Section 5.8). ν_{max} (nujol) 1715, 1271, 811, ONO_2; 1588, 1557 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.19, d, 3H, $J_{iPr\text{-}Me,H}$ 6.6 Hz, iPr-Me; 1.29, d, 3H, $J_{iPr\text{-}Me,H}$ 7.0 Hz, iPr-Me; 2.07, s, 3H, 6-Me; 3.18, sept., 1H, iPr-H; 5.68, d, 1H, $J_{H4,H5}$ 11.6 Hz, H4; 6.01, d, 1H, $J_{H5,H4}$ 11.6 Hz, H5; 7.42, s, 1H, H2. ^{13}C n.m.r. ($CDCl_3$) δ 16.67, 17.15, $CH(\underline{C}H_3)_2$; 19.87, 6-Me; 32.24, $\underline{C}H(CH_3)_2$; 74.79, C5; 79.51, C4; 86.43, C6; 93.18, C3; 128.07, C2; 151.24, C1.§

Initial assignment of the stereochemistry at the various chiral centres was made on the basis of the results from selected n.O.e. experiments (Figure 5.1), with the overall structure being confirmed by single crystal X-ray structure analysis.

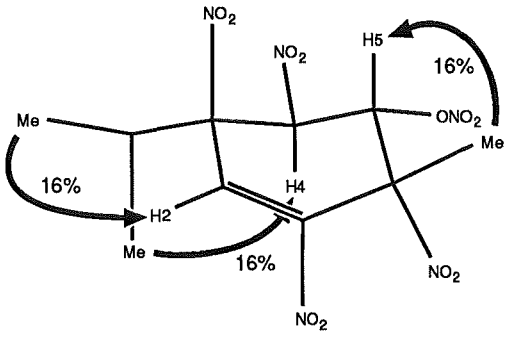


Figure 5.1 Observed n.O.e. enhancements for compound (410).

The ether soluble washings from the above crystals were found to contain small amounts of the three other compounds (411), (412) and (413), which had co-crystallized with compound (410). These compounds were isolated by a combination of h.p.l.c. using hexane/propan-2-ol (82:18) as the eluting solvent, and fractional crystallization from dichloromethane/petroleum ether mixtures.

r-3-hydroxy-6-methyl-3-(methylethyl)-t-5-nitrato-1,c-4,t-6-trinitrocyclo-hexene **(411)** (4%) m.p. 115-116° (dec.) (structure determination by single crystal X-ray analysis, see Section 5.8). ν_{max} (nujol) 3350, OH; 1688, 1267, 812, ONO_2; 1566, 1547 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.14, d, 3H, $J_{iPr\text{-}Me,H}$ 7.0 Hz, iPr-Me; 1.23, d, 3H, $J_{iPr\text{-}Me,H}$ 6.8 Hz, iPr-Me; 2.00, s, 3H, 6-Me; 2.30, sept., 1H, iPr-H; 5.53, d, 1H, $J_{H4,H5}$ 11.4 Hz, H4; 6.37, d, 1H, $J_{H5,H4}$ 11.4 Hz, H5; 7.39, s, 1H, H2. ^{13}C n.m.r. ($CDCl_3$) δ 15.62, 17.16, $CH(\underline{C}H_3)_2$; 20.06, 6-Me; 33.81, $\underline{C}H(CH_3)_2$; 70.40, C3; 76.10, C5; 82.60, C4; 85.83, C6; 134.57, C2.

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* Percentages refer to percentage composition from the original reaction product mixture.

§ XCORFE experiments were used to assist chemical shift assignments.

Initial assignment of the stereochemistry at the various chiral centres was made on the basis of the results from selected n.O.e. experiments (Figure 5.2), with the overall structure being confirmed by single crystal X-ray structure analysis.

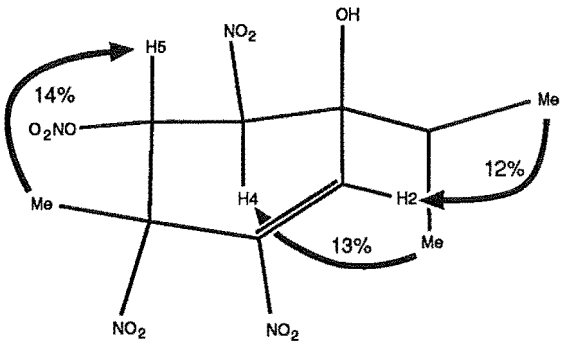

Figure 5.2 Observed n.O.e. enhancements for compound (411).

***6-methyl-3-(methylethyl)-t-5-nitrato-r-3,c-4,t-6-trinitrocyclohexene* (412)** (4%) m.p. 145-146° (structure determination by single crystal X-ray analysis, see Section 5.8). ν_{max} (KBr disk) 1690, 1285, 813, ONO_2; 1574, 1553 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.08, d, 3H, $J_{iPr\text{-}Me,H}$ 6.6 Hz, iPr-Me; 1.25, d, 3H, $J_{iPr\text{-}Me,H}$ 7.0 Hz, iPr-Me; 1.92, s, 3H, 6-Me; 3.13, sept., 1H, iPr-H; 5.94, d, 1H, $J_{H4,H5}$ 11.7 Hz, H4; 5.97, d, 1H, $J_{H5,H4}$ 11.7 Hz, H5; 6.18, d, 1H, $J_{H1,H2}$ 10.1 Hz, H1; 6.24, d, 1H, $J_{H2,H1}$ 10.1 Hz, H2. ^{13}C n.m.r. ($CDCl_3$) δ 16.97, 17.30, $CH(\underline{C}H_3)_2$; 22.51, 6-Me; 31.70, $\underline{C}H(CH_3)_2$, 75.00, C5; 81.05, C4; 88.34, C6; 95.52, C3; 125.47, C2; 133.95, C1.*

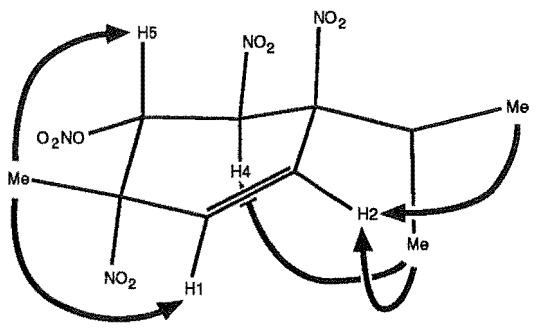

Figure 5.3 Observed n.O.e. enhancements for compound (412).

The stereochemistry at the various chiral centres was assigned on the basis of the results from n.O.e. experiments (Figure 5.3), and the overall structure confirmed by single crystal X-ray structure analysis.

***t-5-acetato-6-methyl-3-(methylethyl)-1,r-3,c-4,t-6-tetranitrocyclohexene* (413)** (4%) m.p. 134-136° (structure determination by single crystal X-ray analysis, see Section 5.8). ν_{max} (nujol) 1789, C=O; 1584, 1571, 1563, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.16, d, 3H, $J_{iPr\text{-}Me,H}$ 6.6 Hz, iPr-Me; 1.25, d, 3H, $J_{iPr\text{-}Me,H}$ 7.1 Hz, iPr-Me; 1.98, s, 3H, 6-Me; 2.08, s, 3H, $COC\underline{H}_3$, 3.13, sept., 1H, iPr-H; 5.66, d, 1H, $J_{H4,H5}$ 11.6 Hz, H4; 5.96, d, 1H, $J_{H5,H4}$ 11.6 Hz, H5; 7.40, s, 1H, H2. ^{13}C n.m.r. ($CDCl_3$) δ 16.72, 17.11, $CH(\underline{C}H_3)_2$; 20.17, $CO\underline{C}H_3$;

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* HETCOR experiments were used to confirm chemical shift assignments.

20.27, 6-Me; 32.30, $\underline{C}H(CH_3)_2$, 67.81, C5; 80.85, C4; 86.92, C6; 92.73, C3; 127.90, C2; 167.93, $\underline{C}OCH_3$.§

The stereochemistry at the various chiral centres was assigned on the basis of the results from selected n.O.e. experiments (Figure 5.4), and the overall structure confirmed by X-ray crystal structure analysis.

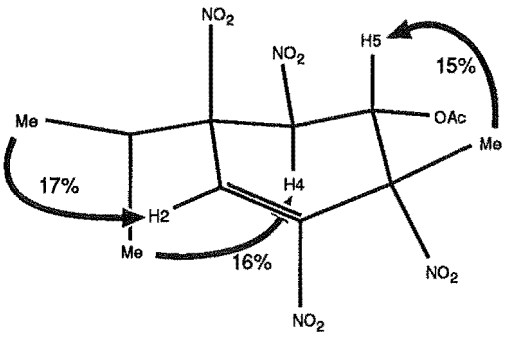

Figure 5.4 Observed n.O.e. enhancements for compound (413).

In the course of separating compounds (411), (412) and (413) above, a further compound (422) was isolated. It was eluted from the h.pl.c. column in hexane/propan-2-ol (85:15). None of the ^1H n.m.r. spectrum resonances for compound (422) were observed in the ^1H n.m.r. spectrum of the original product mixture, indicating that compound (422) is a product of rearrangement, probably formed during the course of the chromatographic separation.

2,5-dinitro-*p*-cymene (422) m.p. 75-76° (lit.[81] 77-78°). ν_{max} (KBr disk) 1636, aromatic; 1530, 1352 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.32, d, 6H, $J_{iPr\text{-}Me,H}$ 6.7 Hz, iPr-methyls; 2.61, s, 3H, Me; 3.37, sept., 1H, iPr-H; 7.64, s, 1H, H6; 8.02, s, 1H, H3.*

5.1.2 Isolation of compounds (403), (405) and (414)-(421)

The residue from the above, initial crystallization was partitioned on the basis of its solubility in pentane, by stirring the mixture overnight in pentane. The pentane soluble fraction (940 mg) was a yellow oil, which was shown (^1H n.m.r.) to contain only two major compounds. Separation by chromatography on silica, using a Chromatotron, and eluting with pentane yielded the two aromatic compounds 2-nitro-*p*-cymene (403) and *p*-nitrotoluene (405).

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§ HETCOR experiments were used to confirm chemical shift assignments.

* Selected n.O.e. difference experiments confirmed the assignments for H3 and H6.

2-nitro-*p*-cymene (403) (25%). ν_{max} (liquid film) 2960, C-H; 1530, 1345, NO_2; 833, 805 cm^{-1} (lit.[95] 2965, 1529, 1347, 832, 804 cm^{-1}). ^1H n.m.r. ($CDCl_3$) δ 1.27, d, 6H, $J_{iPr\text{-}Me,H}$ 6.9 Hz, iPr-methyls; 2.55, s, 3H, Me; 2.96, sept., 1H, iPr-H,; 7.25, d, 1H, $J_{H6,H5}$ 7.9 Hz, H6; 7.37, dd, $J_{H5,H6}$ 7.9 Hz, $J_{H5,H3}$ 1.9 Hz, H5; 7.83, d, $J_{H3,H5}$ 1.9 Hz, H3 (lit.[96] δ 1.26, d, 6H; 2.54, s, 3H; 2.95, sept., 1H). ^{13}C n.m.r. ($CDCl_3$) δ 19.90, Me; 23.58, $CH(\underline{C}H_3)_2$; 33.41, $\underline{C}H(CH_3)_2$; 122.33, C3; 130.70, C1; 131.24, C6; 132.59, C5; 148.07, C4 (lit.[97] δ 19.8, 23.6, 33.5, 122.4, 130.7, 131.3, 132.8, 148.2).

***p*-nitrotoluene (405)** (8%) m.p. 49-51° (lit.[98] 54.5°). ν_{max} (nujol) 1598, aromatic; 1511, 1346, NO_2; 1108, 735 cm^{-1} (lit.[99] 1599, 1517, 1345, 1109, 737 cm^{-1}). ^1H n.m.r. ($CDCl_3$) δ 2.47, s, 3H, Me; 7.33, d, 2H, $J_{H2,H3}$ 8.8 Hz, H2 and H6; 8.11, d, 2H, $J_{H3,H2}$ 8.8 Hz, H3 and H5 (lit.[100] δ 2.48, s, 3H; 7.33, d, 2H; 8.11, d, 2H). ^{13}C n.m.r. ($CDCl_3$) δ 21.59, Me; 123.51, C3 and C5; 129.78, C2 and C6 (lit.[101] δ 21.4, 123.5, 130.0).

The pentane insoluble fraction was a viscous orange/red oil (2.25g). Attempts to separate the components of this mixture at room temperature, using a Chromatotron equipped with a silica gel plate, resulted in extensive decomposition, with only a very small percentage of the material being eluted from the plate. Consequently, the chromatographic separation was repeated at 0°, with particular emphasis placed on minimizing contact time of the material on the Chromatotron plate. Although some decomposition was still observed, the majority of the material was recovered. Further purification of the fractions thus obtained, by h.p.l.c. on a cyano-propyl column, using hexane/propan-2-ol as the eluting solvents, and subsequent crystallizations, led to the isolation of eight further compounds (listed in elution order from the initial 0° chromatographic separation).

***4-(1-acetato-1-methyl-2-nitroethyl)-toluene* (414)** (3%) (Found: *m/z* 237.1001. $C_{12}H_{15}NO_4$ requires 237.1001). ν_{max} (liquid film) 1746, C=O; 1553, 1374 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.95, s, 3H, 4-(1-Me); 2.13, s, 3H, $COC\underline{H}_3$; 2.34, s, 3H, 1-Me; 4.96, d, 1H, $J_{geminal}$ 11.4 Hz, $C\underline{H}_2NO_2$; 5.07, d, 1H, $J_{geminal}$ 11.4 Hz, $C\underline{H}_2NO_2$; 7.19, d, 2H, $J_{H2,H3}$ 8.7 Hz, H2 or H3; 7.21, d, 2H, $J_{H2,H3}$ 8.7 Hz, H2 or H3. ^{13}C n.m.r. ($CDCl_3$) δ 21.00, 1-Me; 21.99, $CO\underline{C}H_3$; 24.34, 4-(1-Me); 80.08, $\underline{C}CH_2NO_2$; 82.02, $\underline{C}H_2NO_2$; 124.24, C3 and C5; 129.53, C2 and C6; 137.17, C4; 138.22, C1; 169.48, $\underline{C}OCH_3$.*

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* XCORFE experiments were used to aid chemical shift assignments.

***4-(1-hydroxy-1-methyl-2-nitroethyl)-toluene* (415)** (3%) (Found: *m/z* 195.0897. $C_{10}H_{13}NO_3$ requires 195.0895). ν_{max} (liquid film) 3570, OH; 1561, 1387 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.63, s, 3H, 4-(1-Me); 2.35, s, 3H, 1-Me; 4.63, d, 1H, $J_{geminal}$ 12.6 Hz, $C\underline{H}_2NO_2$; 4.76, d, 1H, $J_{geminal}$ 12.6 Hz, $C\underline{H}_2NO_2$; 7.19, d, 2H, $J_{H2,H3}$ 8.3 Hz, H2 and H6; 7.34, d, 2H, $J_{H2,H3}$ 8.3 Hz, H3 and H5. ^{13}C n.m.r. ($CDCl_3$) δ 20.98, 1-Me; 27.62, 4-(1-Me); 73.32, $\underline{C}CH_2NO_2$; 84.70, $\underline{C}H_2NO_2$; 124.45, C3 and C5; 129.44, C2 and C6; 137.82, C1; 139.61, C4.1§

***c-5-acetato-6-methyl-3-(methylethyl)-1,r-3,t-4,c-6-tetranitrocyclohexene* (416)** (<1%) (only very small quantities were isolated, not totally pure). ^1H n.m.r. ($CDCl_3$) δ 1. 12, d, 3H, $J_{iPr\text{-}Me,H}$ 6.7 Hz, iPr-Me; 1.28, d, 3H, $J_{iPr\text{-}Me,H}$ 6.8 Hz, iPr-Me; 1.91, s, 3H, 6-Me; 2.11, s, 3H, $COC\underline{H}_3$; 2.94, sept., 1H, iPr-H; 5.68, d, 1H, $J_{H4,H5}$ 11.5 Hz, H4; 6.14, d, 1H, $J_{H5,H4}$ 11.5 Hz, H5; 7.67, s, 1H, H2.

In the absence of a single crystal X-ray structure analysis, assignment of stereochemistry at the various chiral centres was made solely on the basis of the results from selected n.O.e. experiments (Figure 5.5).

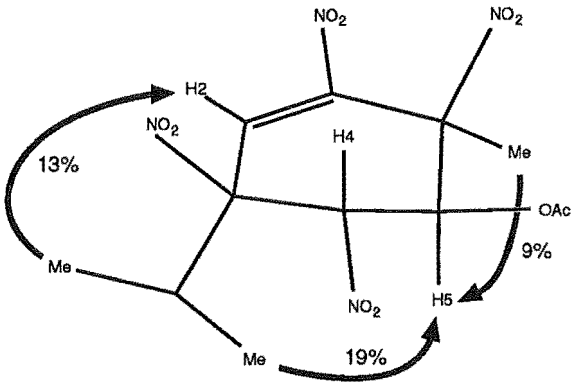

Figure 5.5 Observed n.O.e. enhancements for compound (416).

***t-5-acetato-r-3-hydroxy-6-methyl-3-(methylethyl)-1,c-4,t-6-trinitrocyclohexene* (417)** (<1%) m.p. 165-166° (structure determination by single crystal X-ray analysis, see Section 5.8). ν_{max} (KBr disk) 3480, OH; 1750, C=O; 1575, 1551, 1374, 1348, cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.11, d, 3H, $J_{iPr\text{-}Me,H}$ 7.0 Hz, iPr-Me; 1.21, d, 3H, $J_{iPr\text{-}Me,H}$ 6.8 Hz, iPr-Me; 1.91, s, 3H, 6-Me; 2.10, s, 3H, $COC\underline{H}_3$; 2.17, sept., 1H, iPr-H; 5.52, d, 1H, $J_{H4,H5}$ 11.4 Hz, H4; 6.27, d, 1H, $J_{H5,H4}$ 11.4 Hz, H5; 7.38, s, 1H, H2. ^{13}C n.m.r. ($CDCl_3$) δ 15.69, 17.12, $CH(\underline{C}H_3)_2$; 20.29, $CO\underline{C}H_3$; 20.52, 6-Me; 34.31, $\underline{C}H(CH_3)_2$; 69.05, C5; 73.74, C3; 83.86, C4; 87.23, C6; 134.67, C2; 168.69, $\underline{C}OCH_3$.*

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§ XCORFE and HETCOR experiments were used to confirm chemical shift assignments.

* HETCOR experiments were used to confirm chemical shift assignments.

The stereochemistry at the various chiral centres was assigned on the basis of the results from selected n.O.e. experiments (Figure 5.6), and the overall structure confirmed by single crystal X-ray structure analysis.

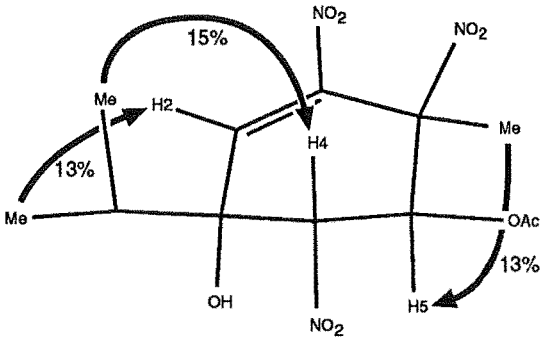

Figure 5.6 Observed n.O.e. enhancements for compound (417).

***r-3-hydroxy-4-methyl-1-(methylethyl)-t-5-nitrato-t-4,c-6-dinitrocyclohexene* (418)** (5%) (Found: *m/z* 305.0866. $C_{10}H_{15}N_3O_8$ requires 305.0859). ν_{max} (liquid film) 3550, OH; 1670, 1280, 813, ONO_2; 1568, 1348 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.07, d, 3H, $J_{iPr\text{-}Me,H}$ 6.9 Hz, iPr-Me; 1.15, d, 3H, $J_{iPr\text{-}Me,H}$ 6.6 Hz, iPr-Me; 1.79, s, 3H, 4-Me; 2.25, sept., 1H, iPr-H; 2.65, s, 1H, OH; 4.81, bd, 1H, $J_{H3,H2}$ 4.4 Hz, H3; 5.62, bd, 1H, $J_{H6,H5}$ 5.7 Hz, H6; 6.00, bd, 1H, $J_{H2,H3}$ 4.4 Hz, H2; 6.37, d, 1H, $J_{H5,H6}$ 5.7 Hz, H5. ^{13}C n.m.r. ($CDCl_3$) δ 18.84, 4-Me; 20.29, 22.00, $CH(\underline{C}H_3)_2$; 30.51, $\underline{C}H(CH_3)_2$; 68.52, C3; 78.31, C5; 86.91, C6; 90.66, C4; 125.39, C2; 141.06, C1.*

In the absence of a single crystal X-ray structure analysis, the stereochemistry at the various chiral centres was assigned on the basis of the results from selected n.O.e. experiments (Figure 5.7), and by comparisons of these results with similar results for the closely related compounds (435) and (419).

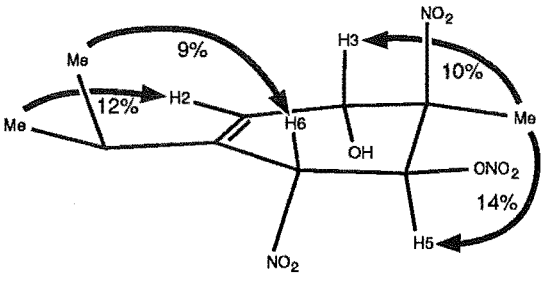

Figure 5.7 Observed n.O.e. enhancements for compound (418).

***6-methyl-3-(methylethyl)-c-5-nitrato-1,r-3,t-4,c-6-tetranitrocyclohexene* (420)** (4%) m.p. 130.5-131° (dec.) (structure determination by single crystal X-ray analysis, see Section 5.8). ν_{max} (KBr disk) 1692, 1278, 800, ONO_2; 1583, 1567 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.16, d, 3H, $J_{iPr\text{-}Me,H}$ 6.7 Hz, iPr-Me; 1.30, d, 3H, $J_{iPr\text{-}Me,H}$ 6.8 Hz, iPr-Me; 2.01, s, 3H, 6-Me; 2.94, sept., 1H, iPr-H; 5.76, d, 1H, $J_{H4,H5}$ 11.7 Hz, H4; 6.19, d, 1H, $J_{H5,H4}$ 11.7 Hz, H5;

7.65, s, 1H, H2. ^{13}C n.m.r. ($CDCl_3$) δ 18.49, 19.18, $CH(\underline{C}H_3)_2$; 19.91, 6-Me; 34.80, $\underline{C}H(CH_3)_2$; 75.90, C5; 83.48, C4; 85.37, C6; 92.28, C3; 130.98, C2.*

The stereochemistry at the various chiral centres was assigned on the basis of the results from selected n.O.e. experiments (Figure 5.8), and the overall structure confirmed by single crystal X-ray structure analysis.

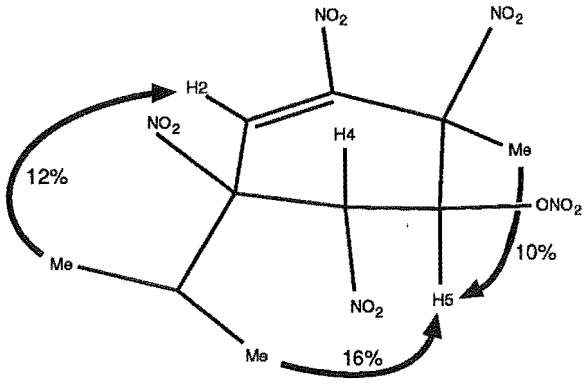

Figure 5.8 Observed n.O.e. enhancements for compound (420).

***r-3-hydroxy-4-methyl-1-(methylethyl)-c-5-nitrato-c-4,t-6-dinitrocyclohexene* (419)** (5%) m.p. 143-145° (dec.) (structure determination by single crystal X-ray analysis, see Section 5.8). ν_{max} (nujol) 3350, OH; 1687, 1274, 824, ONO_2; 1576, 1554 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.11, d, 3H, $J_{iPr\text{-}Me,H}$ 6.7 Hz, iPr-Me; 1.12, d, 3H, $J_{iPr\text{-}Me,H}$ 6.8 Hz, iPr-Me; 1.88, s, 3H, 4-Me; 2.22, sept., 1H, iPr-H; 2.83, d, 1H, $J_{OH,H3}$ 10.6 Hz, OH; 4.69, bd, 1H, $J_{H3,OH}$ 10.6 Hz, H3; 5.75, bd, 1H, $J_{H6,H5}$ 7.5 Hz, H6; 5.81, bs, 1H, H2; 6.06, d, 1H, $J_{H5,H6}$ 7.5 Hz, H5. ^{13}C n.m.r. ($CDCl_3$) δ 19.28, 20.37, 21.95, methyls; 29.96, $\underline{C}H(CH_3)_2$; 71.55, C3; 79.48, C5; 88.50, C6; 92.09, C4; 127.12, C2; 139.55, C1.

The results from selected n.O.e. experiments were used to assign the stereochemistry at the various chiral centres (Figure 5.9), and the overall structure was confirmed by single crystal X-ray structure analysis.

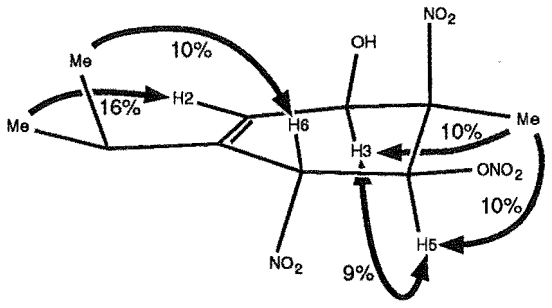

Figure 5.9 Observed n.O.e. enhancements for compound (419).

***6-methyl-3-(methylethyl)-t-5-nitrato-1,r-3,c-4,c-6-tetranitrocyclohexene* (421)** (1%) m.p. 133-135° (dec.) (structure determination by single crystal X-ray analysis, see Section 5.8). ν_{max} (KBr disk) 1725, 1284, 810, ONO_2;

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* HETCOR experiments were used to confirm chemical shift assignments.

1580, 1558,1350 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.14, d, 3H, $J_{iPr\text{-}Me,H}$ 7.0 Hz, iPr-Me; 1.18, d, 3H, $J_{iPr\text{-}Me,H}$ 6.6 Hz, iPr-Me; 2.06, s, 3H, 6-Me; 3.18, sept., 1H, iPr-H; 5.11, d, 1H, $J_{H4,H5}$ 11.7 Hz, H4; 6.31, d, 1H, $J_{H5,H4}$ 11.7 Hz, H5; 7.53, s, 1H, H2. ^{13}C n.m.r. ($CDCl_3$) δ 16.89, 17.20, $CH(\underline{C}H_3)_2$; 18.34, 6-Me; 32.64, $\underline{C}H(CH_3)_2$; 75.32, C5; 80.65, C4; 86.59, C6; 92.75, C3; 126.75, C2; 142.70, C1.*

The stereochemistry at the various chiral centres was assigned on the basis of the results from selected n.O.e. experiments (Figure 5.10), and the overall structure confirmed by single crystal X-ray structure analysis.

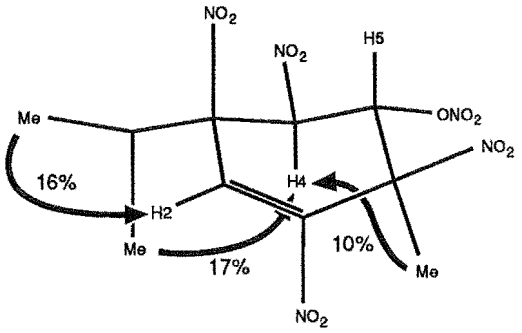

Figure 5.10 Observed n.O.e. enhancements for compound (421).

5.2 REACTION OF *P*-CYMENE WITH NO_2 IN CH_2Cl_2

A solution of *p*-cymene (2g) in dichloromethane (2ml) was de-oxygenated by a stream of pure nitrogen. Nitrogen dioxide was bubbled through the solution at 0-5° for 30 seconds, and the resulting solution stirred under an atmosphere of nitrogen dioxide for 24 hours at room temperature. Following reaction, the excess nitrogen dioxide was removed in a stream of nitrogen, and the solvent removed under reduced pressure. The residue was an orange/red oil (1.24g), which was shown (^1H n.m.r.) to be a very complex mixture.

5.2.1 Isolation of compounds (403), (405), (423) and (426)

Initial separation of the mixture was effected by chromatography at 0°, using a Chromatotron equipped with a silica gel plate, and eluting with petroleum

* HETCOR experiments were used to confirm chemical shift assignments.

ether/ether solvent mixtures. Although a large number of fractions were collected, over a wide solvent polarity range, the separation achieved was poor, and only the major product of reaction [compound (423)] was isolated pure.

***p*-methylacetophenone (423)**

(33%) (Found: [M+H] *m/z* 135.0814. $C_9H_{11}O$ requires 135.0810). ν_{max} (liquid film) 1682, C=O; 1608, 1250, 810 cm^{-1} (lit.[102] 1682, 1607, 1268, 815 cm^{-1}). ^1H n.m.r. ($CDCl_3$) δ 2.41, s, 3H, 4-Me; 2.57 (shift variable), s, 3H, CO<u>Me</u>; 7.26, d, 2H, $J_{H3,H2}$ 8.3 Hz, H3 and H5; 7.86, d, 2H, $J_{H2,H3}$ 8.3 Hz, H2 and H6. ^1H n.m.r. (CCl_4, 60 MHz) δ 2.38, s, 3H; 2.49, s, 3H; 7.16, d, 2H; 7.75, d, 2H (lit.[103] δ 2.38, s, 3H; 2.49, s, 3H; 7.16, d, 2H; 7.75, d, 2H.). ^{13}C n.m.r. ($CDCl_3$) δ 21.52, 4-Me; 26.41, CO<u>C</u>H_3; 128.35, C2 and C6; 129.16, C3 and C5; 134.65, C1; 143.80, C4; 197.76, C=O. ^{13}C n.m.r. (CCl_4) δ 21.40, 25.82, 128.12, 128.79, 134.84, 142.63, 194.76 (lit.[104] δ 22.10, 26.70, 129.0, 129.7, 135.5, 143.6, 196.0).

Although the separation observed on the Chromatotron was not sufficient to yield pure samples of the compounds of interest, many of the fractions obtained were very simple mixtures, containing only two or three compounds. Further separation of these fractions was achieved by h.p.l.c., using hexane/dichloromethane solvent mixtures. These subsequent separations enabled the isolation of pure samples of three further compounds.

2-nitro-*p*-cymene (403) (5%). The sample was identical in all respects (i.r., n.m.r.) with an authentic sample (for spectroscopic data see Section 5.1.1).

***p*-nitrotoluene (405)** (3%). The sample was identical in all respects (i.r., n.m.r.) with an authentic sample (for spectroscopic data see Section 5.1.1).

***4-(1-methyl-1-"X"ethyl)-toluene* (426)**

(11%) (Found: [M-X] *m/z* 133, $C_{10}H_{13}$). ν_{max} (liquid film) 2950, CH; 1566, 1328 cm^{-1}. ^1H n.m.r. ($CDCl_3$) δ 1.81, s, 6H, methyls; 2.36, s, 3H, 1-Me; 7.19, d, 2H, $J_{H2,H3}$ 8.4 Hz, H2 and H6; 7.23, d, 2H, $J_{H3,H2}$ 8.4 Hz, H3 and H5. ^{13}C n.m.r. ($CDCl_3$) δ 21.02, 1-Me; 27.12, C"X"(<u>C</u>H_3)$_2$; 92.15, <u>C</u>"X"(CH_3)$_2$; 125.25, C3 and C5; 129.36, C2 and C6; 138.38, C1; 139.41, C4.*

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* XCORFE experiments were used to confirm chemical shift assignments.

The results from selected n.O.e. difference experiments, in which the ^{1}H n.m.r. resonances corresponding to the two different methyl types of compound (426) were irradiated separately, confirmed the ^{1}H n.m.r. chemical shift assignments for H2 and H6, and H3 and H5 (see Figure 5.11).

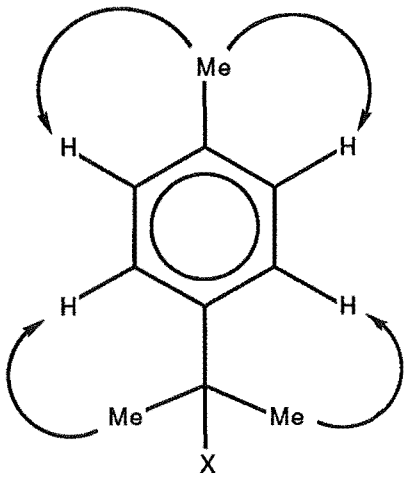

Figure 5.11 Observed n.O.e. enhancements for compound (426).

5.2.2 Separation of compounds (424) and (425)

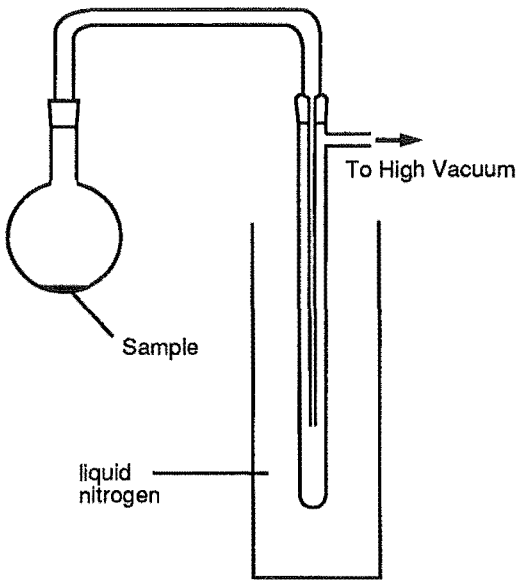

Figure 5.12 Vacuum distillation setup for separating compounds (424) and (425).

In addition to the above three compounds, h.p.l.c. yielded a further fraction, shown to be a mixture (c. 1:1) of two compounds. These compounds were separated on the basis of their differing volatilities, as it was found that one compound was quite volatile under high vacuum (< 1mm Hg) pressures, at room temperature. Compound (424) was subsequently isolated by distillation under vacuum.

(p-methylbenzoic acid, nitric acid) mixed anhydride (424)

(12%) (Found: *m/z* 136, $C_8H_8O_2$; 119, C_8H_7O). ν_{max} (liquid film) 1700, 1630, 1283, 857, 760 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$) δ 2.49, s, 3H, 4-Me; 7.40, d, 2H, $J_{H3,H2}$ 8.3 Hz, H3 and H5; 8.04, d, 2H, $J_{H2,H3}$ 8.3 Hz, H2 and H6. ^{13}C

n.m.r. ($CDCl_3$) δ 22.12, 4-Me; 130.24, C3 and C5; 130.62, C2 and C6; 131.17, C1; 148.76, C4; 167.39, C=O.§

Selected n.O.e. experiments, in which the ^1H n.m.r. resonances corresponding to the two different methyl types were irradiated separately, confirmed the ^1H n.m.r. chemical shift assignments for H2 and H6, and H3 and H5 (see Figure 5.13).

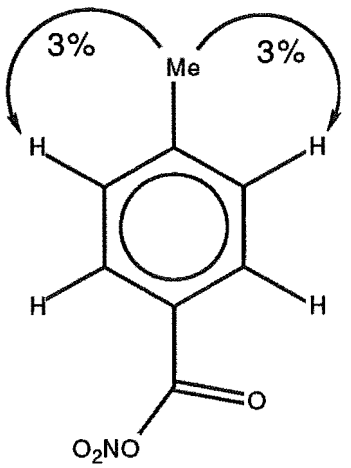

Figure 5.13 Observed n.O.e. enhancements for compound (424).

The residue from the vacuum distillation was pure compound (425).

***4-(1-methyl-1-nitroethyl)-toluene* (425)**

(6%). ν_{max} (liquid film) 1543, 1526, 1355, 1272, 854, 823 cm^{-1} (lit.[89] ν_{max} ($CHCl_3$) 1540, 1530, 1510, 1365, 1280, 850, 820 cm^{-1}). ^1H n.m.r. ($CDCl_3$) δ 1.98, s, 6H, methyls; 2.35, s, 3H, 1-Me; 7.19, d, 2H, $J_{H2,H3}$ 8.3 Hz, H2 and H6; 7.32, d, 2H, $J_{H3,H2}$ 8.3 Hz, H3 and H5 (lit.[90] δ 1.96, s, 6H; 2.34, s, 3H; 7.17, d, 2H; 7.32, d, 2H.). ^{13}C n.m.r. ($CDCl_3$) δ 21.00, 1-Me; 27.30, $CNO_2(\underline{C}H_3)_2$; 89.65, $\underline{C}NO_2(CH_3)_2$; 125.14, C3 and C5; 129.37, C2 and C6; 137.33, C1; 138.79, C4.

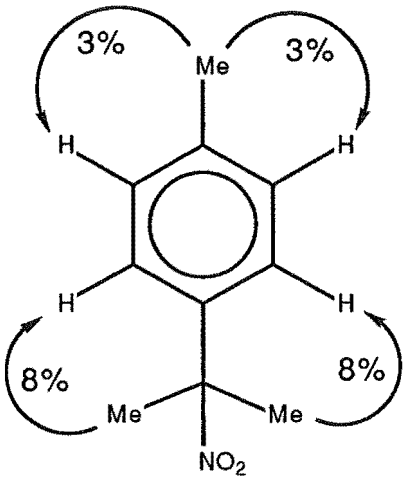

Figure 5.14 Observed n.O.e. enhancements for compound (426).

Selected n.O.e. difference experiments, involving separate irradiation at the two methyl reonances (Figure 5.14) of compound (425), confirmed the ^1H n.m.r. chemical shift assignments for H2 and H6, and H3 and H5.

§ XCORFE experiments were used to confirm chemical shift assignments.

5.2.3 Identification of compound (415)

The only other compound successfully identified in the ^{1}H n.m.r. spectrum of the crude reaction mixture was ***4-(1-hydroxy-1-methyl-2-nitroethyl)-toluene***, compound (415) (6%). Although it was not isolated pure in this case, it was identified on the basis of its ^{1}H n.m.r. resonances (see Section 5.1.2), in an initial Chromatotron fraction which contained substantial amounts of the compound.

5.3 *CIS* AND *TRANS* NITRO ACETOXY CYCLOHEXA-2,5-DIENES

A cold solution of nitric acid (20ml) in acetic anhydride (75ml), was added slowly, with stirring, to a solution of *p*-cymene (42g) in acetic anhydride (85ml) at -45°. The mixture was allowed to warm to -15°, and maintained at that temperature for 9 hours.[86] After reaction was complete, the mixture was cooled to -70°, 400ml of cold ether added, and ammonia condensed into the solution. Excess ammonia was removed in a stream of nitrogen, and the mixture poured into iced water. The combined ether extracts were washed with water, dried ($MgSO_4$), and the ether evaporated to give a yellow oil (65g) containing approximately 65% of diene adducts. The remaining 35% consisted mainly of 2-nitro-*p*-cymene (403) (23%), and *p*-nitrotoluene (405) (10%). The two diastereoisomeric dienes (431) and (432) were separated from the aromatic compounds by chromatography on silica at 0°, using a Chromatotron, and eluting with ether/petroleum ether solvent mixtures.

The initial fractions, eluted in 100% petroleum ether yielded pure samples of both 2-nitro-*p*-cymene (403) and *p*-nitrotoluene (405), with spectroscopic data identical to that of authentic samples. Elution with 20% ether/petroleum ether gave the two cyclohexa-2,5-dienes (431) and (432).[86]

r-1-acetato-4-methyl-1-(methylethyl)-t-4-nitrocyclohexa-2,5-diene (431)
^{1}H n.m.r. ($CDCl_3$) δ 0.88, d, 6H, $J_{iPr\text{-}Me,H}$ 6.9 Hz, iPr-Me; 1.79, s, 3H, 4-Me; 2.00, s, 3H, $OCOC\underline{H}_3$; 2.04, sept., 1H, iPr-H; 5.95, d, 2H, $J_{H2,H3}$ 10.3 Hz, H2 and H6; 6.22, d, 2H, $J_{H3,H2}$ 10.3 Hz, H3 and H5 (lit.[86] δ 0.88, d, 6H; 1.79, s, 3H; 2.00, s, 3H; 2.05, sept., 1H; 5.96, d, 2H; 6.21, d, 2H).

r-1-acetato-4-methyl-1-(methylethyl)-c-4-nitrocyclohexa-2,5-diene (432)
^{1}H n.m.r. ($CDCl_3$) δ 0.88, d, 6H, $J_{iPr\text{-}Me,H}$ 7.0 Hz, iPr-Me; 1.71, s, 3H, 4-Me; 1.98, s, 3H, $OCOC\underline{H}_3$; 2.20, sept., 1H, iPr-H; 6.05, d, 2H, $J_{H2,H3}$ 10.5 Hz, H2 and H6; 6.33, d, 2H, $J_{H3,H2}$ 10.5 Hz, H3 and H5 (lit.[86] δ 0.89, d, 6H; 1.71, s, 3H; 1.97, s, 3H; 2.21, sept., 1H; 6.05, d, 2H; 6.33, d, 2H).

5.4 *TRANS* HYDROXY NITRO CYCLOHEXA-2,5-DIENE

The crude product from the nitric acid nitration of *p*-cymene (above, 5g) was treated with 1.5 molar equivalents of sodium methoxide in methanol, and stirred at -5° for 2 hours.[86] The resulting red solution was diluted with water, and extracted with ether. The ether solution was washed, dried ($MgSO_4$), and the solvent removed under reduced pressure to give a dark red oil (2.9g), the major component of which was shown to be the hydroxy nitro diene (433). The diene was purified by chromatography at 0°, using a Chromatotron equipped with a silica gel plate and eluting with 50% ether/ petroleum ether.

r-1-hydroxy-4-methyl-1-(methylethyl)-t-4-nitrocyclohexa-2,5-diene (433)
^{1}H n.m.r. ($CDCl_3$) δ 0.88, d, 6H, $J_{iPr\text{-}Me,H}$ 6.9 Hz, iPr-Me; 1.76, s, 3H, 4-Me; 1.87, septet, 1H, iPr-H; 6.02, d, 2H, $J_{H2,H3}$ 10.3 Hz, H2 and H6; 6.12, d, 2H, $J_{H3,H2}$ 10.3 Hz, H3 and H5 (lit.[86] δ 0.87, d, 6H; 1.74, s, 3H; 1.8, m, 1H; 6.02, d, 2H; 6.11, d, 2H). ^{13}C n.m.r. ($CDCl_3$) δ 16.76, $CH(\underline{C}H_3)_2$; 27.22, 4-Me; 36.75, $\underline{C}H(CH_3)_2$; 70.42, C1; 83.78, C4; 126.83, 135.02, C2, C3, C5, and C6.

5.5 REACTION OF CYCLOHEXA-2,5-DIENES WITH NO_2 IN Ac_2O

All three of the above cyclohexa-2,5-dienes (431), (432) and (433) were reacted under the same conditions. The diene (200mg) was dissolved in acetic anhydride (1ml) and de-oxygenated by a stream of pure nitrogen. Nitrogen dioxide was bubbled through the solution for 30 seconds, and the resulting solution stirred under an atmosphere of nitrogen dioxide for 24 hours. Excess nitrogen dioxide was removed in a stream of nitrogen, and

the solvent removed under reduced pressure. The yellow/orange oils thus formed were analyzed by ^{1}H n.m.r spectroscopy.

(i) Reaction of diene (431) under the above conditions gave a yellow oil (253mg), shown (^{1}H n.m.r.) to be a very complex mixture. The composition of this mixture was found to be very similar to the composition of the product mixture obtained from the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride. In fact, all the products formed had been previously isolated and characterized from the *p*-cymene reaction. Compounds (410), (412), (418), (403), (419), (420), (411), (413), (421), (416) and (417) were identified in the ^{1}H n.m.r. spectrum of the crude reaction product mixture of the cyclohexa-2,5-diene (431) in approximate ratios of 22:10:10:9:9:8:6:3:3:1:1 respectively. These compounds were able to be isolated in an identical manner to that described above (see Section 5.1), and were identical in all respects (n.m.r., m.p., i.r.) with authentic material.

(ii) Reaction of diene (432) under the above conditions gave a yellow oil (249mg), shown (^{1}H n.m.r.) to be a very complex mixture. The composition of this mixture was found once again to be very similar to the composition of the product mixture obtained from the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride. Compounds (410), (403), (412), (418), (419), (420), (411), (413), (421), (416) and (417) were identified in the ^{1}H n.m.r. spectrum of the crude reaction product mixture of the cyclohexa-2,5-diene (432) in approximate ratios of 26:12:9:9:7:6:6:5:3:1:1 respectively. These compounds were able to be isolated in an identical manner to that described above (see Section 5.1), and were identical in all respects (n.m.r., m.p., i.r.) with authentic material.

(iii) Reaction of diene (433) under the above conditions gave a yellow oil (269mg), the composition of which was shown (^{1}H n.m.r.) once again to be very similar to the composition of the product mixture obtained from the reaction of *p*-cymene with nitrogen dioxide in acetic anhydride. Compounds (403), (410), (418), (412), (419), (420), (411), (413), (421), (416) and (417) were identified in the ^{1}H n.m.r. spectrum of the crude reaction product mixture of the cyclohexa-2,5-diene (433) in approximate ratios of 20:15:6:5:5:4:4:2:2:1:1 respectively.

5.6 NITRATION OF CYCLOHEXA-2,5-DIENE (431) IN CH_2Cl_2

The diene (431) (100mg), in dichloromethane (1ml) was de-oxygenated by a stream of pure nitrogen. The solution was cooled to 0°, and nitrogen dioxide bubbled through the solution for 30 seconds. The resulting brown solution was stirred, at 0°, under an atmosphere of nitrogen dioxide for three hours. Following reaction, the reaction flask was placed immediately under high vacuum (< 1mm Hg), to remove the solvent and any excess nitrogen dioxide. The crude product thus formed was a light yellow oil (140mg). Analysis of this oil by ^1H n.m.r. spectroscopy indicated the presence of five compounds, the mixture consisting substantially (> 60%) of two compounds (434) and (435) (*c.* 1:1), with lesser amounts of 2-nitro-*p*-cymene (403) (4%), compound (412) (8%) and one other compound (438) (8%). Crystallization of the crude product oil from dichloromethane/hexane yielded white crystals.

4-methyl-1-(methylethyl)-c-5-nitrato-r-3,c-4,t-6-trinitrocyclohexene **(435)** m.p. 93.5-94° (very unstable compound. Crystals were unsuitable for single crystal X-ray structure analysis). ν_{max} (KBr disk) 2980, C-H; 1681, 1265, 818, ONO_2; 1569, 1556 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.19, d, 3H, $J_{iPr\text{-}Me,H}$ 6.7 Hz, iPr-Me; 1.22, d, 3H, $J_{iPr\text{-}Me,H}$ 6.8 Hz, iPr-Me; 2.09, s, 3H, 4-Me; 2.30, sept., 1H, iPr-H; 5.58, m, 1H, H3; 5.78, dm, 1H, $J_{H6,H5}$ 8.2 Hz, H6; 6.10, d, 1H, $J_{H5,H6}$ 8.2 Hz, H5; 6.13, m, 1H, H2. ^{13}C n.m.r. ($CDCl_3$) δ 20.25, 20.53, 21.79, methyls; 30.53, $\underline{C}H(CH_3)_2$; 78.72, C5; 85.60, C3; 87.51, C6; 116.66, C1; 117.63, C2.§

The assignment of the stereochemistry at the various chiral centres was made on the basis of the results from selected n.O.e. difference experiments (Figure 5.15), and by comparisons of chemical shift and coupling constant data, with similar data for the related compounds (419) and (434).

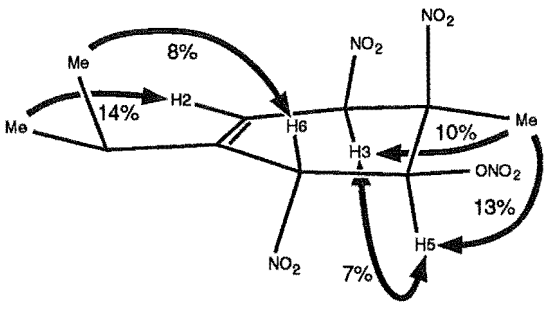

Figure 5.15 Observed n.O.e. enhancements for compound (435).

§ HETCOR experiments were used to assist carbon chemical shift assignments.

Separation of the residue from the above crystallization was achieved by h.p.l.c. on a cyano-propyl column, using hexane/dichloromethane (85:15) as the eluting solvent system. This enabled the isolation of the other major component of the original product mixture. Subsequent crystallization from dichloromethane/hexane yielded white crystals of compound (434).

4-methyl-1-(methylethyl)-t-5-nitrato-r-3,t-4,c-6-trinitrocyclohexene **(434)** m.p. 85-86° (structure determination by single crystal X-ray analysis, see Section 5.8). ν_{max} (liquid film) 1678, 1264, 809, ONO_2; 1564, 1330 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.13, d, 3H, $J_{iPr\text{-}Me,H}$ 6.9 Hz, iPr-Me; 1.17, d, 3H, $J_{iPr\text{-}Me,H}$ 6.7 Hz, iPr-Me; 1.88, s, 3H, 4-Me; 2.36, sept., 1H, iPr-H; 5.76, dm, 1H, $J_{H6,H5}$ 7.5 Hz, H6; 5.82, bd, 1H, $J_{H3,H2}$ 5.4 Hz, H3; 6.04, dm, 1H, $J_{H2,H3}$ 5.4 Hz, H2; 6.79, d, 1H, $J_{H5,H6}$ 7.5 Hz, H5. ^{13}C n.m.r. ($CDCl_3$) δ 19.28, 4-Me; 20.17,22.17, $CH(\underline{C}H_3)_2$; 31.01, $\underline{C}H(CH_3)_2$; 76.58, C5; 86.05, 86.12, C3 and C6; 87.83, C4; 116.63, C2; 118.16, C1.*

Initial assignment of the stereochemistry at the various chiral centres was made on the basis of the results from selected n.O.e. experiments (Figure 5.16), with the overall structure being confirmed by single crystal X-ray structure analysis.

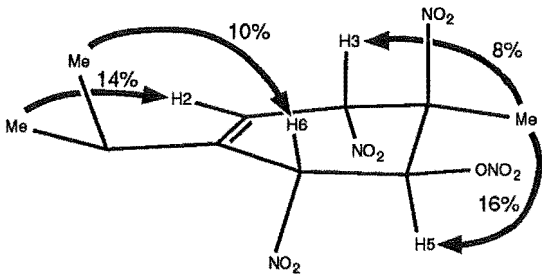

Figure 5.16 Observed n.O.e. enhancements for compound (434).

Although a pure sample of compound (438) was not isolated, h.p.l.c. enabled the separation of an approximately 70% pure fraction, from which extensive n.m.r. spectroscopic information was obtained. On the basis of this spectroscopic data, a tentative structure was assigned for compound (438).

4-methyl-1-(methylethyl)-r-3,t-5-dinitrato-t-4,c-6-dinitrocyclohexene **(438)** (a pure sample was not obtained. Spectroscopic data was obtained from a slightly contaminated mixture). ν_{max} (liquid film) 1666, 1656, 1280, 825, ONO_2; 1560, 1542, 1353 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.09, d, 3H, $J_{iPr\text{-}Me,H}$ 7.0 Hz, iPr-Me; 1.16, d, 3H, $J_{iPr\text{-}Me,H}$ 6.7 Hz, iPr-Me; 1.81, s, 3H, 4-Me; 2.30, sept., 1H, iPr-H; 5.66, bd, 1H, $J_{H6,H5}$ 6.5 Hz, H6; 5.97, dm, 1H, $J_{H2,H3}$ 5.0 Hz, H2; 6.14, d, 1H, $J_{H3,H2}$ 5.0 Hz, H3; 6.24, d, 1H, $J_{H5,H6}$ 6.5 Hz,

* HETCOR experiments were used to assist carbon chemical shift assignments.

H5. ^{13}C n.m.r. ($CDCl_3$) δ 18.82, 4-Me; 20.26,22.08, $CH(\underline{C}H_3)_2$; 30.92, $\underline{C}H(CH_3)_2$; 75.96, C3; 77.77, C5; 85.95, C6; 88.41, C4; 119.71, C2.*

The assignment of the stereochemistry at the various chiral centres was made on the basis of the results from selected n.O.e. experiments (Figure 5.17), and by comparisons of chemical shift and coupling constant data, with similar data for the related compounds (418) and (434).

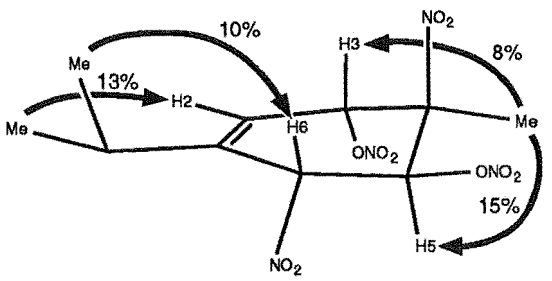

Figure 5.17 Observed n.O.e. enhancements for compound (438).

During the course of isolating compounds (434) and (438) by h.p.l.c., a further compound (439) was isolated. This compound is not observed in the ^1H n.m.r. spectrum of the original product mixture, and is thought to arise from rearrangement of compound (435), during the chromatographic separation. Compound (439) was isolated and purified by h.p.l.c., using hexane/dichloromethane (85:15) as the eluting solvent mixture.

***4-methyl-1-(methylethyl)-r-5-nitrato-3,t-6-dinitrocyclohexa-1,3-diene* (439)**
(this compound is quite unstable, and quickly rearranges to 2,5-dinitro-*p*-cymene (422). The structural assignment was based solely on spectroscopic evidence). ν_{max} (liquid film) 1662, 1282, 827, ONO_2; 1561, 1536, 1350 cm^{-1}, NO_2. ^1H n.m.r. ($CDCl_3$) δ 1.12, d, 3H, $J_{iPr\text{-}Me,H}$ 6.8 Hz, iPr-Me; 1.21, d, 3H, $J_{iPr\text{-}Me,H}$ 6.8 Hz, iPr-Me; 2.27, s, 3H, 4-Me; 2.64, sept., 1H, iPr-H; 5.24, d, 1H, $J_{H6,H5}$ 2.5 Hz, H6; 6.19, d, 1H, $J_{H5,H6}$ 2.5 Hz, H5; 6.62, bs, 1H, H2. ^{13}C n.m.r. ($CDCl_3$) δ 17.81, 4-Me; 20.11, 21.27, $CH(\underline{C}H_3)_2$; 32.34, $\underline{C}H(CH_3)_2$; 79.15, C5; 82.24, C6; 118.16, C2; 127.20, 138.86, C1 and C4; 147.30, C3.*

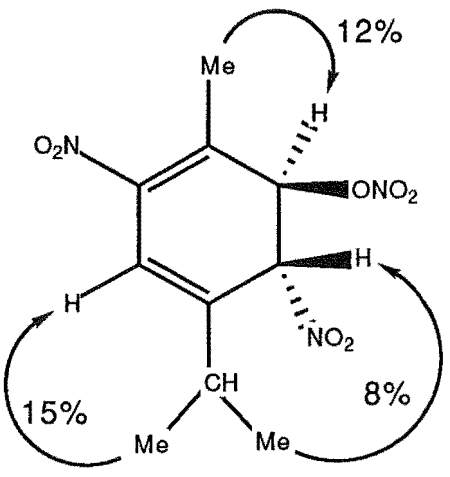

Figure 5.18 Observed n.O.e. enhancements for compound (439).

* HETCOR experiments were used to assist carbon chemical shift assignments.

Due to the instability of the compound, a single crystal X-ray structure analysis was not feasible. Similarly, elemental mass analysis also proved difficult. Consequently, selected n.O.e. experiments (Figure 5.18, above) were used to confirm the chemical shift assignments, and to assist with the determination of the overall structure.

5.7 THE NITRATION OF COMPOUNDS (434), (435) AND (439) IN ACETIC ANHYDRIDE

To determine the stability of compounds (434), (435) and (439) under the reaction conditions of nitrogen dioxide in acetic anhydride, all three compounds were reacted under the following conditions. A sample of the compound in acetic anhydride (1ml) was de-oxygenated by a stream of nitrogen. Nitrogen dioxide was bubbled through the solution for 30 seconds, and the resulting solution stirred under an atmosphere of nitrogen dioxide for 24 hours at room temperature. Excess nitrogen dioxide was removed in a stream of nitrogen, and the solvent removed under reduced pressure to give the crude product. Analysis of the composition of the mixture was by ^{1}H n.m.r. spectroscopy.

(i) Reaction of compound (435) (10mg) under the above conditions, gave a mixture (*c.* 4:1:1:1) of the four compounds (410), (411), (421) and (420) respectively, all of which had been previously isolated and characterized (see Section 5.1). Crystallization of the crude mixture from dichloromethane/hexane yielded crystals of compound (410), identical in all respects (m.p., n.m.r.) with authentic material.

(ii) Reaction of compound (434) (8mg) under the above conditions resulted in only partial reaction after 24 hours. Analysis by ^{1}H n.m.r. spectroscopy at this point, indicated a mixture (*c.* 30:10:5:2:2:1) of compounds (434) (unreacted starting material), (410), (422), (411), (420) and (421) respectively.

(iii) Reaction of compound (439) (40mg) under the above conditions gave a mixture (*c.* 9:2:4:3) of compounds (410), (411), (421) and (420) respectively.

5.8 SINGLE CRYSTAL X-RAY ANALYSES : PART TWO

The data sets used for the single crystal X-ray structure analyses of compounds (410), (411), (412), (413), (417), (419), (420), (421) and (434) were collected on a Nicolet R3m four-circle diffractometer, using graphite monochromated Mo-K_α radiation (λ 0.71069 Å). Either Wyckoff or ω–scans were used to collect reflection intensities out to a Bragg angle θ, given below. The space group was in each case, determined on the basis of systematic absences of appropriate reflections. The cell parameters were determined by least squares refinement of at least 23 accurately centred reflections. Crystal stability was monitored by recording three check reflections every 100 reflections. The data sets were corrected for Lorentz and polarization effects but absorption corrections were not applied.

Crystal data for 6-methyl-3-(methylethyl)-*t*-5-nitrato-1,*r*-3,*c*-4,*t*-6-tetranitrocyclohexene (410) - $C_{10}H_{13}N_5O_{11}$, M 379.24, monoclinic, space group $P2_1/c$, a 10.670(2), b 11.325(2), c 14.266(3) Å, β 117.29(1) °, U 1532.0 Å^3, D_m 1.63 g cm^{-3}, D_c 1.65 g cm^{-3}, Z 4, μ(Mo K_α) 1.41 cm^{-1}. The crystal was colourless and of approximate dimensions 0.26 by 0.48 by 0.60 mm. Data was collected at a temperature of 163K using the ω-scan technique. A total of 2946 reflections were collected, out to a maximum Bragg angle (θ) 27°. Of these reflections, 2844 were unique, and 2306 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0004; R-factor 0.0358; wR 0.0384.

Crystal data for *r*-3-hydroxy-6-methyl-3-(methylethyl)-*t*-5-nitrato-1,*c*-4,*t*-6-trinitrocyclohexene (411) - $C_{10}H_{14}N_4O_{10}$, M 350.24, orthorhombic, space group $Pbcn$, a 18.108(4), b 9.603(2), c 16.749(5) Å, U 2912.5 Å^3, D_m 1.54 g cm^{-3}, D_c 1.59 g cm^{-3}, Z 8, μ(Mo K_α) 1.36 cm^{-1}. The crystal was pale yellow and of approximate dimensions 0.30 by 0.71 by 0.72 mm. Data was collected at a temperature of 173K using the ω-scan technique. A total of 3382 reflections were collected, out to a maximum Bragg angle (θ) 26°. Of these reflections, 2886 were unique, and 1770 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0016; R-factor 0.0454; wR 0.0451.

Crystal data for 6-methyl-3-(methylethyl)-*t*-5-nitrato-*r*-3,*c*-4,*t*-6-trinitrocyclohexene (412) - $C_{10}H_{14}N_4O_9$, M 318.24, triclinic, space group $P\bar{1}$, a 9.706(2), b 11.567(4), c 13.776(4) Å, α 80.83(2), β 79.68(2), γ 70.13(2) °, U 1423.1 Å^3, D_m 1.47 g cm^{-3}, D_c 1.48 g cm^{-3}, Z 4, μ(Mo K_α) 1.30 cm^{-1}. The crystal

was colourless and of approximate dimensions 0.23 by 0.52 by 0.77 mm. Data was collected at a temperature of 173K using the ω-scan technique. A total of 4535 reflections were collected, out to a maximum Bragg angle (θ) 24°. Of these reflections, 4363 were unique, and 2807 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0003; R-factor 0.0389; wR 0.0380.

The structure consists of two, well separated, crystallographically independent molecules. Superposition of the two molecules , using the SHELXTL[79] program XFIT (Figure 4.7), revealed no gross differences of any chemical significance between the two molecules.

Crystal data for *t*-5-acetato-6-methyl-3-(methylethyl)-1,*r*-3,*c*-4,*t*-6-tetranitrocyclohexene (413) - $C_{12}H_{16}N_4O_{10}$, M 376.28, monoclinic, space group $P2_1$, a 8.109(1), b 12.057(2), c 8.671(2) Å, β 104.22(2) °, U 821.7 Å^3, D_m 1.50 g cm^{-3}, D_c 1.52 g cm^{-3}, Z 2, μ(Mo K_α) 0.59 cm^{-1}. The crystal was colourless and of approximate dimensions 0.18 by 0.30 by 0.59 mm. Data was collected at a temperature of 173K using the ω-scan technique. A total of 2063 reflections were collected, out to a maximum Bragg angle (θ) 27°. Of these reflections, 1871 were unique, and 1714 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.00049; R-factor 0.0314; wR 0.0336.

Crystal data for *t*-5-acetato-*r*-3-hydroxy-6-methyl-3-(methylethyl)-1,*c*-4,*t*-6-trinitrocyclohexene (417) - $C_{12}H_{17}N_3O_9$, M 347.28, triclinic, space group $P\bar{1}$, a 8.422(1), b 8.201(1), c 12.012(2) Å, α 90.14(1), β 104.07(1), γ 100.93(1) °, U 789.1 Å^3,D_m 1.59 g cm^{-3}, D_c 1.62 g cm^{-3}, Z 2, μ(Mo K_α) 1.19 cm^{-1}. The crystal was colourless and of approximate dimensions 0.32 by 0.32 by 0.60 mm. Data was collected at a temperature of 298K using the Wyckoff scan technique. A total of 2130 reflections were collected, out to a maximum Bragg angle (θ) 22°. Of these reflections, 2053 were unique, and 1460 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0002; R-factor 0.0402; wR 0.0415.

Crystal data for *r*-3-hydroxy-4-methyl-1-(methylethyl)-*c*-5-nitrato-*c*-4,*t*-6-dinitrocyclohexene (419) - $C_{10}H_{15}N_3O_8$, M 305.24, triclinic, space group $P\bar{1}$, a 6.690(2), b 8.940(3), c 11.737(3) Å, α 98.00(2), β 91.02(2), γ 105.03(2) °, U 670.2 Å^3, D_m 1.50 g cm^{-3}, D_c 1.51 g cm^{-3}, Z 2, μ(Mo K_α) 1.24 cm^{-1}. The crystal was colourless and of approximate dimensions 0.15 by 0.20 by 0.40 mm. Data was collected at a temperature of 173K using the ω-scan technique. A total of 1815 reflections were collected, out to a maximum

Bragg angle (θ) 22°. Of these reflections, 1716 were unique, and 823 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0003; R-factor 0.0327; ωR 0.0344.

Crystal data for 6-methyl-3-(methylethyl)-*c*-5-nitrato-1,*r*-3,*t*-4,*c*-6-tetranitrocyclohexene (420) - $C_{10}H_{13}N_5O_{11}$, M 379.24, monoclinic, space group $P2_1/n$, a 15.260(4), b 12.071(4), c 18.125(8) Å, β 110.76(3) °, U 3121.9 Å^3, D_m 1.58 g cm^{-3}, D_c 1.61 g cm^{-3}, Z 8, μ(Mo K_α) 1.39 cm^{-1}. The crystal was colourless and of approximate dimensions 0.30 by 0.78 by 0.85 mm. Data was collected at a temperature of 183K using the Wyckoff scan technique. A total of 4474 reflections were collected, out to a maximum Bragg angle (θ) 22°. Of these reflections, 4068 were unique, and 2854 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.0003; R-factor 0.0345; ωR 0.0345.

The structure consists of two, well separated, crystallographically independent molecules. Superposition of the two molecules , using the SHELXTL[79] program XFIT (Figure 4.17), revealed no gross differences of any chemical significance between the two molecules.

Crystal data for 6-methyl-3-(methylethyl)-*t*-5-nitrato-1,*r*-3,*c*-4,*c*-6-tetranitrocyclohexene (421) - $C_{10}H_{13}N_5O_{11}$, M 379.24, triclinic, space group $P\bar{1}$, a 6.946(3), b 9.094(4), c 13.493(8) Å, α 82.62(4), β 77.05(4), γ 68.02(3) °, U 769.4 Å^3, D_m 1.62 g cm^{-3}, D_c 1.64 g cm^{-3}, Z 2, μ(Mo K_α) 1.41 cm^{-1}. The crystal was colourless and of approximate dimensions 0.58 by 0.63 by 0.96 mm. Data was collected at a temperature of 173K using the ω-scan technique. A total of 2094 reflections were collected, out to a maximum Bragg angle (θ) 22°. Of these reflections, 2028 were unique, and 1663 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.00033; R-factor 0.0325; ωR 0.0338.

Crystal data for 4-methyl-1-(methylethyl)-*t*-5-nitrato-*r*-3,*t*-4,*c*-6-trinitrocyclohexene (434) - $C_{10}H_{14}N_4O_9$, M 334.24, triclinic, space group $P\bar{1}$, a 7.765(3), b 11.285(3), c 16.915(8) Å, α 84.13(2), β 88.95(3), γ 86.88(2) °, U 1472.2 Å^3, D_m 1.50 g cm^{-3}, D_c 1.51 g cm^{-3}, Z 4, μ(Mo K_α) 1.26 cm^{-1}. The crystal was colourless and of approximate dimensions 0.09 by 0.17 by 0.69 mm. Data was collected at a temperature of 193K using the ω-scan technique. A total of 3908 reflections were collected, out to a maximum Bragg angle (θ) 22°. Of these reflections, 3785 were unique, and 1520 having intensity (I) > 3σ(I) were ultimately used in the structure refinement. g 0.00151; R-factor 0.0408; ωR 0.0425.

The structure consists of two, well separated, crystallographically independent molecules. Superposition of the two molecules , using the SHELXTL[79] program XFIT (Figure 4.27), revealed no gross differences of any chemical significance between the two molecules.

Intensity data were processed, and structure solution and refinement were carried out using a Data General Nova 4X computer, and the SHELXTL[79] system of programs. Diagrams were produced using the SHELXTL graphics program XP and a Tektronix 4113A colour graphics unit.

All the structures determined in this work were solved by direct methods and refined by blocked-cascade least squares techniques. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ where $w = [\sigma^2(F_o) + gF_o^2]^{-1}$. Anomalous dispersion corrections were from Cromer and Libermann.[80] All non-hydrogen atoms were assigned anisotropic thermal parameters, whereas hydrogen atoms were assigned thermal parameters equal to 1.2U of their carrier atoms. Methyl hydrogen atoms were included as rigid groups pivoting about their carbon atoms, with all other hydrogen atoms being included at idealized positions. Final Fourier syntheses showed no significant residual electron density and there were no abnormal discrepancies between observed and calculated structure factors.

Further, more comprehensive material regarding the structural information for the above structures (temperature factors, structure factor amplitudes, interatomic distances, bond angles and torsional angles) is deposited with the Editor-in-Chief, Editorial and Publications Service, CSIRO, 34 Albert Street, East Melbourne, Victoria 3002, Australia.

Table 7. Fractional coordinates for atoms in 6-methyl-3-(methylethyl)-*t*-5-nitrato-1,*r*-3,*c*-4,*t*-6-tetranitrocyclohexene (410)

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U^*
C(1)	-2965(2)	-1777(1)	6916(1)	19(1)
C(2)	-2766(2)	-1010(1)	6304(1)	19(1)
C(3)	-2320(2)	243(1)	6624(1)	19(1)
C(4)	-1629(2)	289(1)	7839(1)	19(1)
C(5)	-2586(2)	-220(1)	8261(1)	20(1)
C(6)	-2968(2)	-1533(1)	7952(1)	21(1)
C(7)	-1393(2)	724(2)	6145(1)	22(1)
C(8)	-2176(2)	789(2)	4946(1)	29(1)
C(9)	-57(2)	-16(2)	6497(2)	29(1)
C(10)	-4350(2)	-1832(2)	7957(2)	31(1)
N(1)	-3231(2)	-3019(1)	6550(1)	24(1)
N(3)	-3668(2)	1018(1)	6222(1)	24(1)
N(4)	-1224(2)	1534(1)	8232(1)	29(1)
N(5)	-2627(2)	526(1)	9854(1)	29(1)
N(6)	-1749(2)	-2245(1)	8810(1)	24(1)
O(11)	-3125(1)	-3764(1)	7201(1)	35(1)
O(12)	-3493(2)	-3230(1)	5643(1)	36(1)
O(31)	-4768(1)	537(1)	6075(1)	32(1)
O(32)	-3546(2)	2060(1)	6109(1)	45(1)
O(41)	-64(2)	1866(1)	8380(1)	43(1)
O(42)	-2082(2)	2120(1)	8365(1)	49(1)
O(51)	-1869(1)	-126(1)	9386(1)	23(1)
O(52)	-1902(1)	667(1)	10768(1)	38(1)
O(53)	-3805(2)	813(2)	9292(1)	47(1)
O(61)	-1976(2)	-2812(1)	9431(1)	38(1)
O(62)	-611(1)	-2156(1)	8811(1)	32(1)

* The equivalent isotropic temperature factor in this and the following Tables is defined as one-third of orthogonalized U tensor (Å2).

Table 8. **Fractional coordinates for atoms in *r*-3-hydroxy-6-methyl-3-(methylethyl)-*t*-5-nitrato-1,*c*-4,*t*-6-trinitrocyclohexene (411)**

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	3612(2)	-1081(3)	5374(2)	18(1)
C(2)	3309(1)	-1126(3)	4661(2)	18(1)
C(3)	3303(1)	-2398(3)	4124(2)	19(1)
C(4)	3858(2)	-3479(3)	4469(2)	20(1)
C(5)	3767(2)	-3620(3)	5369(2)	21(1)
C(6)	3949(2)	-2269(3)	5828(2)	21(1)
C(7)	3484(1)	-1964(3)	3262(2)	23(1)
C(8)	2862(2)	-1102(4)	2892(2)	32(1)
C(9)	4209(2)	-1164(4)	3213(2)	35(1)
C(10)	3668(2)	-2374(3)	6682(2)	33(1)
N(1)	3638(1)	272(2)	5786(1)	22(1)
N(4)	3708(1)	-4872(3)	4081(2)	26(1)
N(5)	3931(2)	-5689(3)	6186(2)	31(1)
N(6)	4796(1)	-2103(3)	5827(2)	28(1)
O(11)	3155(1)	1126(2)	5661(1)	38(1)
O(12)	4162(1)	451(2)	6233(1)	31(1)
O(3)	2601(1)	-3073(2)	4169(1)	22(1)
O(41)	3354(1)	-5736(2)	4458(1)	32(1)
O(42)	3941(1)	-5046(2)	3408(1)	40(1)
O(51)	4261(1)	-4687(2)	5640(1)	25(1)
O(52)	4383(1)	-6479(2)	6424(2)	47(1)
O(53)	3287(1)	-5607(2)	6321(2)	42(1)
O(61)	5085(1)	-1787(3)	5194(1)	39(1)
O(62)	5124(1)	-2310(3)	6448(2)	47(1)

Table 9. Fractional coordinates for atoms in 6-methyl-3-(methylethyl)-*t*-5-nitrato-*r*-3,*c*-4,*t*-6-trinitrocyclohexene (412)

Molecule 1

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	4936(3)	2762(2)	9200(2)	23(1)
C(2)	5673(3)	3546(2)	9129(2)	21(1)
C(3)	6350(3)	4096(2)	8188(2)	19(1)
C(4)	6394(3)	3371(2)	7325(2)	20(1)
C(5)	4965(3)	3085(2)	7357(2)	21(1)
C(6)	4558(3)	2354(2)	8332(2)	21(1)
C(7)	7882(3)	4164(2)	8289(2)	24(1)
C(8)	7781(3)	4994(3)	9076(2)	33(1)
C(9)	8943(3)	2873(3)	8522(2)	37(1)
C(10)	2950(3)	2422(3)	8477(2)	30(1)
N(3)	5348(2)	5446(2)	7977(2)	26(1)
N(4)	6746(2)	4023(2)	6324(2)	28(1)
N(5)	4071(3)	2807(3)	5892(2)	39(1)
N(6)	5539(3)	984(2)	8281(2)	30(1)
O(31)	5797(2)	6088(2)	7297(2)	44(1)
O(32)	4181(2)	5803(2)	8521(2)	40(1)
O(41)	8048(2)	3891(2)	6035(1)	34(1)
O(42)	5735(2)	4624(2)	5858(2)	52(1)
O(51)	5193(2)	2359(2)	6553(1)	29(1)
O(52)	2976(2)	3618(2)	6130(2)	44(1)
O(53)	4438(3)	2228(3)	5197(2)	64(1)
O(61)	6872(2)	773(2)	8138(2)	41(1)
O(62)	4948(2)	202(2)	8382(2)	56(1)

Table 9. cont.

Molecule 2

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1')	1703(3)	8754(2)	5776(2)	25(1)
C(2')	1014(3)	7936(2)	5866(2)	23(1)
C(3')	241(3)	7477(2)	6806(2)	20(1)
C(4')	-12(3)	8357(2)	7604(2)	20(1)
C(5')	1338(3)	8723(2)	7631(2)	21(1)
C(6')	1892(3)	9324(2)	6624(2)	23(1)
C(7')	-1170(3)	7249(2)	6649(2)	25(1)
C(8')	-863(3)	6328(3)	5884(2)	34(1)
C(9')	-2326(3)	8456(3)	6338(2)	36(1)
C(10')	3467(3)	9302(3)	6580(2)	35(1)
N(3')	1325(3)	6213(2)	7181(2)	28(1)
N(4')	-484(3)	7793(2)	8621(2)	29(1)
N(5')	1931(3)	9363(3)	9064(2)	35(1)
N(6')	873(3)	10690(2)	6526(2)	26(1)
O(31')	814(2)	5509(2)	7759(2)	49(1)
O(32')	2630(2)	6005(2)	6888(2)	46(1)
O(41')	-1786(2)	7878(2)	8834(1)	38(1)
O(42')	464(2)	7277(2)	9164(2)	47(1)
O(51')	915(2)	9600(2)	8347(1)	28(1)
O(52')	3017(3)	8484(2)	9003(2)	49(1)
O(53')	1489(3)	10134(2)	9630(2)	50(1)
O(61')	-441(2)	10866(2)	6504(1)	34(1)
O(62')	1407(2)	11506(2)	6472(2)	45(1)

Table 10. Fractional coordinates for atoms in *t*-5-acetato-6-methyl-3-(methylethyl)-1,*r*-3,*c*-4,*t*-6-tetranitrocyclohexene (413)

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	1165(3)	8710(2)	4444(2)	21(1)
C(2)	466(3)	9483(2)	3421(2)	20(1)
C(3)	1075(3)	9777(2)	1973(2)	20(1)
C(4)	2265(3)	8843(2)	1673(2)	20(1)
C(5)	3568(3)	8455(2)	3147(2)	20(1)
C(6)	2731(3)	8032(2)	4470(2)	21(1)
C(7)	-403(3)	10017(2)	495(2)	23(1)
C(8)	-1559(3)	10960(2)	784(3)	31(1)
C(9)	-1461(3)	8979(2)	-39(3)	32(1)
C(10)	6185(3)	7558(2)	3013(3)	25(1)
C(11)	6824(3)	6522(2)	2432(3)	36(1)
C(12)	4032(3)	8053(2)	6066(3)	31(1)
N(1)	329(2)	8466(2)	5737(2)	28(1)
N(3)	2193(2)	10840(2)	2408(2)	24(1)
N(4)	3209(2)	9189(2)	446(2)	27(1)
N(6)	2175(2)	6829(2)	4010(2)	29(1)
O(11)	303(2)	7482(2)	6112(2)	40(1)
O(12)	-290(2)	9223(2)	6322(2)	39(1)
O(31)	2924(2)	10966(2)	3801(2)	36(1)
O(32)	2300(3)	11461(2)	1341(2)	39(1)
O(41)	4537(2)	9705(2)	904(2)	43(1)
O(42)	2577(3)	8930(2)	-924(2)	47(1)
O(51)	4435(2)	7539(1)	2654(2)	23(1)
O(52)	6994(2)	8312(2)	3680(2)	38(1)
O(61)	1011(2)	6717(2)	2812(2)	33(1)
O(62)	2947(3)	6085(2)	4810(3)	48(1)

Table 11. Fractional coordinates for atoms in *t*-5-acetato-*r*-3-hydroxy-6-methyl-3-(methylethyl)-1,*c*-4,*t*-6-trinitrocyclohexene (417)

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	1776(4)	9595(3)	6981(3)	33(1)
C(2)	2788(4)	9090(4)	6435(3)	34(1)
C(3)	3875(3)	7852(3)	6869(2)	32(1)
C(4)	3167(4)	6896(4)	7811(2)	33(1)
C(5)	2864(4)	8052(4)	8690(2)	33(1)
C(6)	1560(4)	9126(4)	8151(3)	34(1)
C(7)	3931(4)	6671(4)	5882(3)	39(1)
C(8)	2205(4)	5724(4)	5254(3)	56(2)
C(9)	4836(5)	7581(4)	5038(3)	59(2)
C(10)	2862(4)	7514(4)	10659(3)	39(1)
C(11)	1999(5)	6375(4)	11386(3)	56(2)
C(12)	1711(4)	10618(4)	8954(3)	47(1)
N(1)	726(4)	10749(3)	6397(2)	46(1)
N(4)	4353(4)	5840(3)	8422(3)	47(1)
N(6)	-173(3)	7966(3)	7996(2)	43(1)
O(11)	1164(3)	11585(3)	5645(2)	64(1)
O(12)	-583(3)	10739(3)	6676(2)	66(1)
O(3)	5542(2)	8711(3)	7316(2)	44(1)
O(41)	5488(3)	6470(3)	9236(2)	60(1)
O(42)	4120(4)	4401(3)	8045(2)	72(1)
O(51)	2237(2)	7035(2)	9524(2)	37(1)
O(52)	3959(3)	8707(3)	10985(2)	51(1)
O(61)	-958(3)	8109(3)	8699(2)	66(1)
O(62)	-610(3)	6925(3)	7199(2)	58(1)

Table 12. **Fractional coordinates for atoms in *r*-3-hydroxy-4-methyl-1-(methylethyl)-*c*-5-nitrato-*c*-4,*t*-6-dinitrocyclohexene (419)**

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	3353(9)	3266(4)	7380(3)	21(2)
C(2)	5320(9)	3642(4)	7129(3)	27(2)
C(3)	6765(7)	5263(4)	7325(3)	26(2)
C(4)	5666(7)	6596(4)	7487(2)	20(2)
C(5)	3891(6)	6127(3)	8277(2)	19(2)
C(6)	2346(6)	4531(3)	7893(2)	21(2)
C(7)	1904(7)	1625(4)	7123(3)	29(2)
C(8)	153(7)	1574(4)	6254(3)	44(2)
C(9)	3030(7)	378(4)	6723(3)	42(2)
C(10)	7185(7)	8151(4)	7959(3)	28(2)
N(4)	4792(5)	6717(3)	6292(2)	28(1)
N(5)	2962(6)	8302(3)	9482(3)	30(2)
N(6)	1299(5)	3995(3)	8973(2)	26(1)
O(3)	8278(4)	5494(3)	6485(2)	32(1)
O(41)	3261(5)	5708(3)	5876(2)	41(1)
O(42)	5721(5)	7776(3)	5795(2)	49(1)
O(51)	2650(4)	7247(2)	8395(2)	26(1)
O(52)	1804(5)	9121(3)	9516(2)	42(1)
O(53)	4298(5)	8222(3)	10163(2)	35(1)
O(61)	2431(4)	3937(3)	9789(2)	34(1)
O(62)	-586(4)	3629(3)	8938(2)	35(1)

Table 13. Fractional coordinates for atoms in 6-methyl-3-(methylethyl)-*c*-5-nitrato-1,*r*-3,*t*-4,*c*-6-tetranitrocyclohexene (420)

Molecule 1

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	9610(2)	6829(2)	1988(2)	16(1)
C(2)	9896(2)	6557(2)	2741(2)	17(1)
C(3)	9320(2)	5948(2)	3127(2)	18(1)
C(4)	8447(2)	5442(2)	2486(2)	18(1)
C(5)	7995(2)	6203(2)	1779(2)	16(1)
C(6)	8669(2)	6596(2)	1365(2)	17(1)
C(7)	9158(2)	6664(2)	3779(2)	24(1)
C(8)	8558(2)	7684(2)	3441(2)	27(1)
C(9)	10092(2)	7019(3)	4401(2)	31(1)
C(10)	8238(2)	7580(2)	832(2)	25(1)
N(1)	10311(2)	7360(2)	1714(1)	20(1)
N(3)	9926(2)	4926(2)	3528(1)	29(1)
N(4)	7710(2)	5099(2)	2824(1)	23(1)
N(5)	6334(2)	6052(2)	984(1)	27(1)
N(6)	8795(2)	5606(2)	862(1)	25(1)
O(11)	10250(1)	7159(2)	1035(1)	29(1)
O(12)	10920(1)	7929(2)	2181(1)	26(1)
O(31)	10478(2)	4591(2)	3226(1)	44(1)
O(32)	9798(2)	4505(2)	4083(1)	51(1)
O(41)	7848(2)	4225(2)	3186(1)	41(1)
O(42)	7032(1)	5701(2)	2722(1)	33(1)
O(51)	7266(1)	5559(2)	1220(1)	21(1)
O(52)	6259(1)	6970(2)	1198(1)	32(1)
O(53)	5763(2)	5419(2)	585(1)	43(1)
O(61)	9195(2)	4793(2)	1230(1)	34(1)
O(62)	8487(2)	5701(2)	149(1)	39(1)

Table 13. cont.

Molecule 2

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1')	7(2)	1853(2)	2048(2)	16(1)
C(2')	367(2)	1562(2)	2793(2)	19(1)
C(3')	1248(2)	910(2)	3155(2)	18(1)
C(4')	1559(2)	433(2)	2491(2)	17(1)
C(5')	1418(2)	1223(2)	1800(2)	18(1)
C(6')	395(2)	1648(2)	1408(2)	17(1)
C(7')	1990(2)	1553(2)	3833(2)	22(1)
C(8')	2313(2)	2610(2)	3539(2)	27(1)
C(9')	1616(2)	1856(3)	4486(2)	37(1)
C(10')	385(2)	2657(2)	904(2)	24(1)
N(1')	-925(2)	2411(2)	1796(1)	21(1)
N(3')	954(2)	-131(2)	3518(1)	27(1)
N(4')	2571(2)	60(2)	2805(1)	23(1)
N(5')	2382(2)	1041(2)	980(1)	27(1)
N(6')	-188(2)	704(2)	885(1)	26(1)
O(11')	-1441(1)	2254(2)	1113(1)	30(1)
O(12')	-1128(1)	2943(2)	2285(1)	26(1)
O(31')	138(2)	-413(2)	3226(1)	48(1)
O(32')	1542(2)	-621(2)	4041(1)	53(1)
O(41')	2722(2)	-852(2)	3115(1)	44(1)
O(42')	3173(1)	671(2)	2734(1)	32(1)
O(51')	1646(1)	583(2)	1225(1)	22(1)
O(52')	2661(1)	1955(2)	1193(1)	31(1)
O(53')	2595(2)	398(2)	571(1)	42(1)
O(61')	-275(1)	-140(2)	1227(1)	35(1)
O(62')	-513(2)	851(2)	176(1)	41(1)

Table 14. Fractional coordinates for atoms in 6-methyl-3-(methylethyl)-*t*-5-nitrato-1,*r*-3,*c*-4,*c*-6-tetranitrocyclohexene (421)

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	3286(3)	6109(2)	3307(1)	21(1)
C(2)	2812(3)	4845(2)	3658(1)	23(1)
C(3)	2329(3)	3846(2)	3013(1)	22(1)
C(4)	3047(3)	4279(2)	1885(1)	21(1)
C(5)	2317(3)	6065(2)	1674(1)	22(1)
C(6)	3443(3)	6781(2)	2228(1)	23(1)
C(7)	3231(3)	2057(2)	3316(1)	23(1)
C(8)	2320(4)	1721(3)	4427(2)	33(1)
C(9)	5631(3)	1427(3)	3130(2)	33(1)
C(10)	5675(3)	6572(3)	1677(2)	32(1)
N(1)	3762(3)	6948(2)	4033(1)	28(1)
N(3)	-113(3)	4349(2)	3215(1)	26(1)
N(4)	2304(3)	3549(2)	1179(1)	29(1)
N(5)	1196(3)	7592(2)	149(1)	30(1)
N(6)	2059(3)	8562(2)	2267(1)	34(1)
O(11)	3433(3)	6566(2)	4934(1)	42(1)
O(12)	4452(2)	7998(2)	3684(1)	38(1)
O(31)	-1168(2)	5579(2)	3642(1)	38(1)
O(32)	-828(2)	3483(2)	2933(1)	36(1)
O(41)	600(2)	4324(2)	941(1)	42(1)
O(42)	3463(3)	2246(2)	886(1)	41(1)
O(51)	2862(2)	6348(2)	602(1)	26(1)
O(52)	-409(2)	8265(2)	703(1)	43(1)
O(53)	1761(2)	7719(2)	-744(1)	41(1)
O(61)	2555(3)	9452(2)	1610(1)	57(1)
O(62)	508(3)	8936(2)	2936(1)	49(1)

Table 15. Fractional coordinates for atoms in 4-methyl-1-(methylethyl)-*t*-5-nitrato-*r*-3,*t*-4,*c*-6-trinitrocyclohexene (434)

Molecule 1

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1)	-2208(7)	1800(4)	-1497(3)	31(2)
C(2)	-3843(7)	1998(5)	-1300(3)	36(2)
C(3)	-4506(6)	2372(4)	-517(3)	30(2)
C(4)	-3137(6)	2165(4)	141(3)	26(2)
C(5)	-1372(6)	2515(5)	-173(3)	29(2)
C(6)	-792(6)	1955(5)	-930(3)	31(2)
C(7)	-1607(7)	1344(5)	-2273(3)	41(2)
C(8)	-2999(8)	1367(7)	-2887(4)	70(3)
C(9)	-707(9)	104(6)	-2140(4)	75(3)
C(10)	-3656(7)	2794(5)	873(3)	40(2)
N(3)	-5099(5)	3701(4)	-629(3)	38(2)
N(4)	-3176(6)	811(4)	385(3)	35(2)
N(5)	717(5)	3097(4)	753(2)	42(2)
N(6)	517(5)	2750(5)	-1362(3)	40(2)
O(31)	-4077(4)	4390(3)	-924(2)	55(2)
O(32)	-6537(4)	3961(4)	-401(2)	60(2)
O(41)	-2001(5)	165(4)	169(2)	52(2)
O(42)	-4397(5)	460(4)	780(3)	67(2)
O(51)	-69(4)	2135(3)	408(2)	37(1)
O(52)	125(5)	4086(3)	589(2)	60(2)
O(53)	1905(4)	2712(4)	1163(2)	60(2)
O(61)	1946(2)	2311(4)	-1500(2)	62(2)
O(62)	48(5)	3786(4)	-1563(2)	58(2)

Table 15. cont.

Molecule 2

Atom	$10^4X/a$	$10^4Y/b$	$10^4Z/c$	10^3U
C(1')	2490(6)	2289(5)	4913(3)	32(2)
C(2')	4035(6)	2458(5)	4585(3)	36(2)
C(3')	4382(6)	3187(5)	3823(3)	35(2)
C(4')	2876(6)	4060(5)	3562(3)	40(2)
C(5')	1169(6)	3450(5)	3673(3)	36(2)
C(6')	879(6)	2855(5)	4509(3)	36(2)
C(7')	2214(7)	1647(5)	5725(3)	43(2)
C(8')	3517(7)	614(5)	5931(4)	56(3)
C(9')	2198(9)	2547(6)	6337(4)	71(3)
C(10')	3110(7)	4688(6)	2722(3)	54(3)
N(3')	4891(7)	2370(4)	3190(3)	48(2)
N(4')	2937(7)	5046(4)	4129(3)	51(2)
N(5')	-1171(6)	4086(5)	2767(3)	55(2)
N(6')	-392(7)	1872(5)	4452(3)	50(2)
O(31')	3769(6)	1831(5)	2919(3)	88(2)
O(32')	6393(5)	2246(4)	3028(3)	69(2)
O(41')	1721(6)	5252(4)	4554(3)	75(2)
O(42')	4251(6)	5588(4)	4118(3)	79(2)
O(51')	-291(4)	4265(3)	3485(2)	49(2)
O(52')	-555(6)	3375(5)	2358(3)	72(2)
O(53')	-2430(4)	4755(4)	2687(3)	75(2)
O(61')	-1728(5)	1941(4)	4818(3)	87(2)
O(62')	55(6)	1077(4)	4059(3)	73(2)

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